CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074229

Trade Name : NADOLOL TABLETS USP

Generic Name:Nadolol Tablets USP

Sponsor : Zenith Goldline Pharmaceuticals, Inc.

Approval Date:August 30, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074229

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074229

APPROVAL LETTER

ANDA 74-229

AUG 30 1996

Zenith Goldline Pharmaceuticals, Inc.
Attention: Joan Janulis
140 LeGrand Avenue
Northvale, NJ 07647

Dear Madam:

This is in reference to your abbreviated new drug application dated June 25, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nadolol Tablets USP, 20 mg and 40 mg.

Reference is also made to your amendments dated January 25, 1993, May 6, 1993, October 28, 1993, January 14, 1994 October 20, 1995, October 25, 1995 and May 2, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Nadolol Tablets USP, 20 mg and 40 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Corgard® Tablets, 20 mg and 40 mg, respectively, of E.R. Squibb and Sons Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

for 8/30/95

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074229

FINAL PRINTED LABELING

NADOLOL
TABLETS, USP

AUG 30 1995

APPROVED

DESCRIPTION

Nadolol is a synthetic nonselective beta-adrenergic receptor blocking agent designated chemically as 1-(*tert*-butylamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol. The structural formula is:

$C_{17}H_{27}NO_4$ M.W. 309.41

Nadolol is a white to off-white, practicaly odorless, crystalline powder. It is freely soluble in water, in alcohol, and in methanol and slightly soluble in chloroform. Nadolol is available for oral administration as 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg tablets and contains the following inactive ingredients: citric acid, colorants (D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, and FD&C Red No. 40 Aluminum Lake), corn starch, magnesium stearate, microcrystalline cellulose and povidone. In addition, the 80 mg, 120 mg and 160 mg tablets contain sodium starch glycolate.

CLINICAL PHARMACOLOGY

Nadolol is a nonselective beta-adrenergic receptor blocking agent. Clinical pharmacology studies have demonstrated beta-blocking activity by showing (1) reduction in heart rate and cardiac output at rest and on exercise, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Nadolol specifically competes with beta-adrenergic receptor agonists for available beta-receptor sites; it inhibits both the $beta_1$ receptors located chiefly in cardiac muscle and the $beta_2$ receptors located chiefly in the bronchial and vascular musculature, inhibiting the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation proportionately. Nadolol has no intrinsic sympathomimetic activity and, unlike some other beta-adrenergic blocking agents, nadolol has little direct myocardial depressant activity and does not have an anesthetic-like membrane-stabilizing action. Animal and human studies show that nadolol slows the sinus rate and depresses AV conduction. In dogs, only minimal amounts of nadolol were detected in the brain relative to amounts in blood and other organs and tissues. Nadolol has low lipophilicity as determined by octanol/water partition coefficient, a characteristic of certain beta-blocking agents that has been correlated with the limited extent to which these agents cross the blood-brain barrier, their low concentration in the brain, and low incidence of CNS-related side effects.

In controlled clinical studies, nadolol at doses of 40 to 320 mg/day has been shown to decrease both standing and supine blood pressure, the effect persisting for approximately 24 hours after dosing.

The mechanism of the antihypertensive effects of beta-adrenergic receptor blocking agents has not been established; however, factors that may be involved include (1) competitive antagonism of catecholamines at peripheral (non-CNS) adrenergic neuron sites (especially cardiac) leading to decreased cardiac output, (2) a central effect leading to reduced tonic-sympathetic nerve outflow to the periphery, and (3) suppression of renin secretion by blockade of the beta-adrenergic receptors responsible for renin release from the kidneys.

While cardiac output and arterial pressure are reduced by nadolol therapy, renal hemodynamics are stable, with preservation of renal blood flow and glomerular filtration rate.

By blocking catecholamine-induced increases in heart rate, velocity and extent of myocardial contraction, and blood pressure, nadolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, nadolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure. Although beta-adrenergic receptor blockade is useful in treatment of angina and hypertension, there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. Beta-adrenergic blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Absorption of nadolol after oral dosing is variable, averaging about 30 percent. Peak serum concentrations of nadolol usually occur in three to four hours after oral administration and the presence of food in the gastrointestinal tract does not affect the rate or extent of nadolol absorption. Approximately 30 percent of the nadolol present in serum is reversibly bound to plasma protein.

Unlike many other beta-adrenergic blocking agents, nadolol is not metabolized by the liver and is excreted unchanged, principally by the kidneys.

The half-life of therapeutic doses of nadolol is about 20 to 24 hours, permitting once-daily dosage. Because nadolol is excreted predominantly in the urine, its half-life increases in renal failure (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Steady-state serum concentrations of nadolol are attained in six to nine days with once-daily dosage in persons with normal renal function. Because of variable absorption and different individual responsiveness, the proper dosage must be determined by titration.

Exacerbation of angina and, in some cases, myocardial infarction and ventricular dysrhythmias have been reported after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with coronary artery disease. Abrupt withdrawal of these agents in patients without coronary artery disease has resulted in transient symptoms, including tremulousness, sweating, palpitation, headache, and malaise. Several mechanisms have been proposed to explain these phenomena, among them increased sensitivity to catecholamines because of increased numbers of beta receptors.

INDICATIONS AND USAGE

Angina Pectoris - Nadolol tablets are indicated for the long-term management of patients with angina pectoris.

Hypertension - Nadolol tablets are indicated in the management of hypertension; it may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

CONTRAINDICATIONS

Nadolol is contraindicated in bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

WARNINGS

Cardiac Failure - Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or nadolol should be discontinued (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal - Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) - PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Nadolol should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery - Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of nadolol can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or norepinephrine. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia - Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis - Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm.

PRECAUTIONS

Impaired Renal Function - Nadolol should be used with caution in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**).

Information for Patients - Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of nadolol therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure. The patient should also be advised of a proper course in the event of an inadvertently missed dose.

Drug Interactions - When administered concurrently, the following drugs may interact with beta-adrenergic receptor blocking agents:

Anesthetics, general - exaggeration of the hypotension induced by general anesthetics (see **WARNINGS, Major Surgery**).

Antidiabetic drugs (oral agents and insulin) - hypoglycemia or hyperglycemia; adjust dosage of antidiabetic drug accordingly (see **WARNINGS, Diabetes and Hypoglycemia**).

Catecholamine-depleting drugs (e.g., reserpine) - additive effect; monitor closely for evidence of hypotension and/or excessive bradycardia (e.g., vertigo, syncope, postural hypotension).

Response to Treatment for Anaphylactic Reaction - While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility - In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, nadolol did not produce any significant toxic effects. In two-year oral carcinogenic studies in rats and mice, nadolol did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, nadolol caused no adverse effects.

Pregnancy Category C - In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose. No teratogenic potential was observed in any of these species. There are no adequate and well-controlled studies in pregnant women. Nadolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonates whose mothers are receiving nadolol at parturition have exhibited bradycardia, hypoglycemia, and associated symptoms.

Nursing Mothers - Nadolol is excreted in human milk. Because of the potential for adverse effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of nadolol to the mother.

Pediatric Use - Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required withdrawal of therapy.

Cardiovascular - Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta blockers (see also **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**).

Central Nervous System - Dizziness or fatigue has been reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior have each been reported in approximately 6 of 1000 patients.

Respiratory - Bronchospasm has been reported in approximately 1 of 1000 patients (See **CONTRAINDICATIONS** and **WARNINGS**).

Gastrointestinal - Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence have been reported in 1 to 5 of 1000 patients.

Miscellaneous - Each of the following has been reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Reversible alopecia has been reported infrequently.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established.

Central Nervous System - Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal - Mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes.

Hematologic - Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Allergic - Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Miscellaneous - Pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with nadolol.

OVERDOSAGE

Nadolol can be removed from the general circulation by hemodialysis.

In addition to gastric lavage, the following measures should be employed, as appropriate. In determining the duration of corrective therapy, note must be taken of the long duration of the effect of nadolol.

Excessive Bradycardia - Administer atropine (0.25 to 1 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure - Administer a digitalis glycoside and diuretic.

It has been reported that glucagon may also be useful in this situation.

Hypotension - Administer vasopressors, e.g., epinephrine or norepinephrine. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm - Administer a beta$_2$-stimulating agent and/or a theophylline derivative.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. NADOLOL MAY BE ADMINISTERED WITHOUT REGARD TO MEALS.

Angina Pectoris - The usual initial dose is 40 mg nadolol once daily. Dosage may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response is obtained or there is pronounced slowing of the heart rate. The usual maintenance dose is 40 or 80 mg administered once daily. Doses up to 160 or 240 mg administered once daily may be needed.

The usefulness and safety in angina pectoris of dosage exceeding 240 mg per day have not been established. If treatment is to be discontinued, reduce the dosage gradually over a period of one to two weeks (see **WARNINGS**).

Hypertension - The usual initial dose is 40 mg nadolol once daily, whether it is used alone or in addition to diuretic therapy. Dosage may be gradually increased in 40 to 80 mg increments until optimum blood pressure reduction is achieved. The usual maintenance dose is 40 or 80 mg administered once daily. Doses up to 240 or 320 mg administered once daily may be needed.

Dosage Adjustment in Renal Failure - Absorbed nadolol is excreted principally by the kidneys and, although nonrenal elimination does occur, dosage adjustments are necessary in patients with renal impairment. The following dose intervals are recommended:

Creatinine Clearance (mL/min/1.73m^2)	Dosage Interval (hours)
> 50	24
31-50	24-36
10-30	24-48
< 10	40-60

HOW SUPPLIED

Available as a green, round tablet debossed "20" on one side, and a bisect on the other side with "Z" on the upper half and "4235" on the lower, containing 20 mg of nadolol, USP packaged in bottles of 100, 500, and 1000 tablets.

Available as a green, round tablet debossed "40" on one side, and a bisect on the other side with "Z" on the upper half and "4236" on the lower, containing 40 mg of nadolol, USP packaged in bottles of 30, 100, 500, and 1000 tablets.

Available as a light green, round tablet debossed "80" on one side, and a bisect on the other side with "Z" on the upper half and "4237" on the lower, containing 80 mg of nadolol, USP packaged in bottles of 30, 100, 500, and 1000 tablets.

Available as a light green, capsule-shaped tablet, partially bisected on both sides, debossed "Z4238" on one side, and "120" on the other side, containing 120 mg of nadolol, USP packaged in bottles of 100, 500, and 1000 tablets.

Available as a green, capsule-shaped tablet, partially bisected on both sides, debossed "Z4239" on one side, and "160" on the other side, containing 160 mg of nadolol, USP packaged in bottles of 100, 500, and 1000 tablets.

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

MANUFACTURED BY
ZENITH LABORATORIES, INC.
NORTHVALE, NEW JERSEY 07647

0172
Revised 09/93
01

NADOLOL TABLETS, USP

Zenith

NDC 0172-4236-46

NADOLOL
TABLETS, USP

40 mg

30 Tablets (Green)

CAUTION: Federal law prohibits dispensing without prescription.

Each Tablet Contains:
Nadolol, USP 40 mg

USUAL DOSAGE: See Package Insert

PHARMACIST:
Dispense in a tight container as defined in the USP. Use child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
ZENITH LABORATORIES, INC.
NORTHVALE, NJ 07647

1192J

N 3 0172-4236-46 2

LOT: SPECIMEN

EXP.

Zenith

NDC 0172-4236-60

NADOLOL
TABLETS, USP

40 mg

100 Tablets (Green)

CAUTION: Federal law prohibits dispensing without prescription.

Each Tablet Contains:
Nadolol, USP 40 mg

USUAL DOSAGE: See Package Insert

PHARMACIST:
Dispense in a tight container as defined in the USP.
Use child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647

1192J

N 3 0172-4236-60 8

LOT: SPECIMEN

EXP.

Zenith

NDC 0172-4236-70

NADOLOL
TABLETS, USP

40 mg

500 Tablets (Green)

CAUTION: Federal law prohibits dispensing without prescription.

Each Tablet Contains:
Nadolol, USP 40 mg

USUAL DOSAGE: See Package Insert

PHARMACIST:
Dispense in a tight container as defined in the USP.
Use child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647

1192J

N 3 0172-4236-70 7

LOT: SPECIMEN

EXP.

Zenith

NDC 0172-4236-80

NADOLOL
TABLETS, USP

40 mg

1000 Tablets (Green)

CAUTION: Federal law prohibits dispensing without prescription.

Each Tablet Contains:
Nadolol, USP 40 mg

USUAL DOSAGE: See Package Insert

PHARMACIST:
Dispense in a tight container as defined in the USP.
Use child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647

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LOT: SPECIMEN

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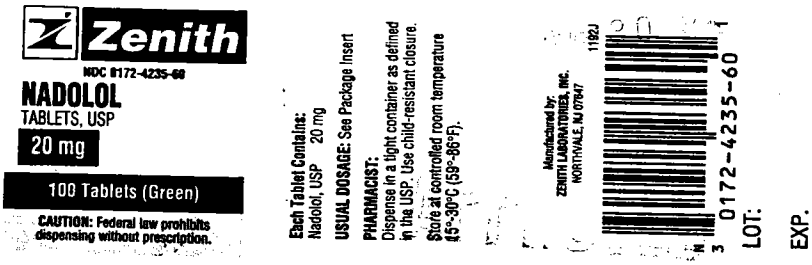
Zenith
NDC 0172-4235-60
NADOLOL
TABLETS, USP
20 mg
100 Tablets (Green)
CAUTION: Federal law prohibits dispensing without prescription.
Each Tablet Contains:
Nadolol, USP 20 mg
USUAL DOSAGE: See Package Insert
PHARMACIST:
Dispense in a tight container as defined in the USP. Use child-resistant closure.
Store at controlled room temperature 15°-30°C (59°-86°F).
Manufactured by:
ZENITH LABORATORIES, INC.
NORTHVALE, NJ 07647
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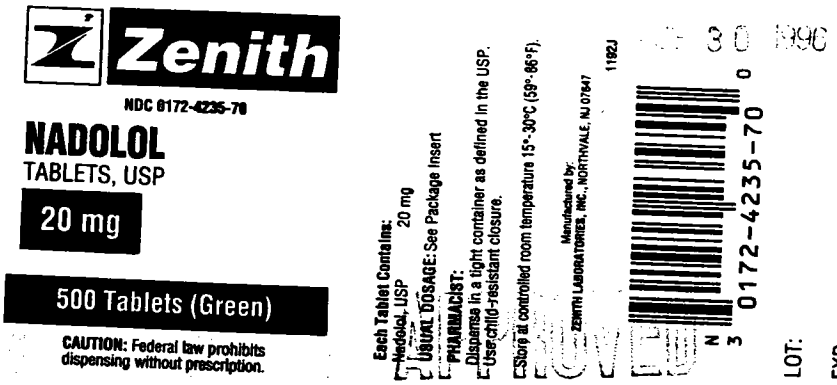
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NDC 0172-4235-70
NADOLOL
TABLETS, USP
20 mg
500 Tablets (Green)
CAUTION: Federal law prohibits dispensing without prescription.
Each Tablet Contains:
Nadolol, USP 20 mg
USUAL DOSAGE: See Package Insert
PHARMACIST:
Dispense in a tight container as defined in the USP.
Use child-resistant closure.
Store at controlled room temperature 15°-30°C (59°-86°F).
Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647
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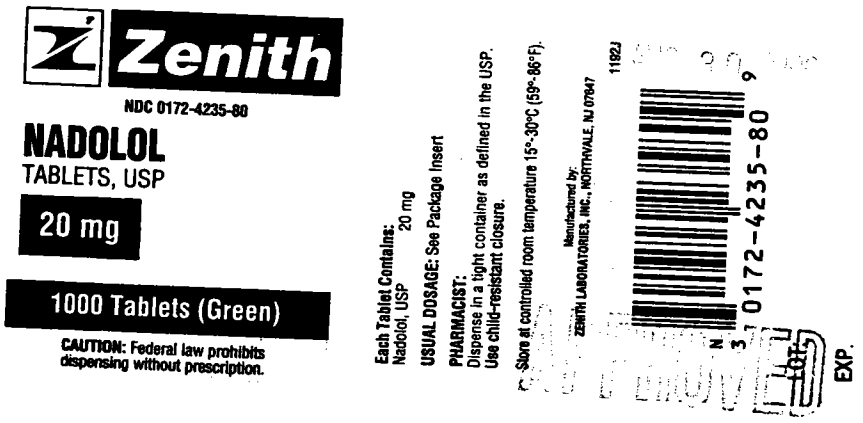
Zenith
NDC 0172-4235-80
NADOLOL
TABLETS, USP
20 mg
1000 Tablets (Green)
CAUTION: Federal law prohibits dispensing without prescription.
Each Tablet Contains:
Nadolol, USP 20 mg
USUAL DOSAGE: See Package Insert
PHARMACIST:
Dispense in a tight container as defined in the USP.
Use child-resistant closure.
Store at controlled room temperature 15°-30°C (59°-86°F).
Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647
1192J
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EXP.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074229

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 5

2. ANDA # 74-229 (20 mg & 40 mg)

3. NAME AND ADDRESS OF APPLICANT
Zenith Laboratories Inc.
140 LeGrand Avenue
Northvale, NJ 07647

4. LEGAL BASIS for ANDA SUBMISSION
In the firms opinion and to the best of its knowledge there are two patents which claim the listed drug, and pharmaceutical formulations containing the listed drug.
Patent # 3,935,267 Expired 1/27/93
Patent # 3,982,021 Expired 9/21/93

Innovator: Squibb - Corgard®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Nadolol

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
6/25/92 - Original (74-229, all 5 strengths)
8/14/92 - Original (2 strengths, split 74-255 with 3 strengths).
1/25/93 - O/NC, Bio. study protocol.
4/28/93 - Response to 1st def. letter (chem. & labeling).
5/6/93 - O/NC, Bio. study.
9/15/93 - Response to 2nd def. letter (chem. & labeling).
10/28/93 - O/NC, Bio. study.
1/14/94 - O/NC, Bio. amendment.
3/31/94 - O/NC, change in manufacturing from DMF.
3/5/95 - O/NC, Bio. information.
10/20/95 - O/NC, response to Bio. letter dated 10/18/94.
10/23/95 - O/NC, Bio. information.
10/25/95 - Response to 4th def. letter.
10/25/95 - O/NC, Bio. information.
3/11/96 - O/NC, change of ownership.
5/2/96 - Response to Bio. letter.

FDA:
7/14/92 - Refuse to file, not common formulation.
9/2/92 - Acknowledgement
11/12/92 - 1st def. letter (chem. & labeling).
11/23/92 - Phone memo, regarding Bio. study protocol.

4/19/93 - Bio. review of protocol
8/18/93 - 2nd def. letter (chem. & labeling).
10/1/93 - 3rd review, no letter.
8/23/94 - Unacceptable Bio. review.
9/15/94 - Unacceptable Bio. review.
10/18/94 - Bio. def. letter.
10/25/94 - 4th def. letter (Bio. & CGMP).
3/26/96 - Unacceptable Bio. review.
4/3/96 - Bio. def. letter.
7/25/96 - Acceptable Bio. review.

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

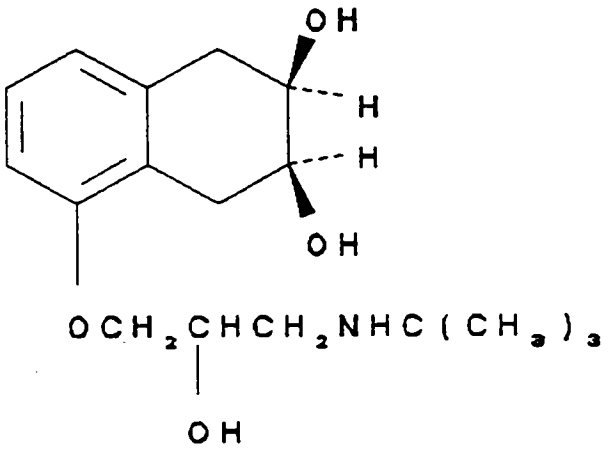
13. DOSAGE FORM
Tablet

14. POTENCIES
20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE

Nadolol USP

$C_{17}H_{27}NO_4$; M.W. = 309.41



(±)-1-(*tert*-Butylamino)-3-[(5,6,7,8-tetrahydro-*cis*-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol. CAS [42200-33-9]

16. RECORDS AND REPORTS
N/A

17. COMMENTS

Bio., EER and DMF's satisfactory. Method validation not required, product is USP.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER: Norman Gregory

DATE COMPLETED: 8/1/96 (Chem.)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074229

BIOEQUIVALENCE REVIEW(S)

APR 19 1993

Nadolol
Tablets, 20 mg and 40 mg
ANDA #74-229
Reviewer: L.A. Ouderkirk
WP #74229P.193

Zenith Laboratories, Inc.
Northvale, New Jersey
Submission Date:
January 25, 1993

Review of a Protocol for a Post-Prandial Bioequivalence Study

BACKGROUND:

The firm has submitted a protocol for a full, 36 subject two-way post-prandial bioequivalence study to be conducted on its nadolol tablets, 40 mg, to be conducted at The firm has already conducted a fasted in-vivo bioequivalence study on its nadolol tablets, 160 mg, (submission dated 11/9/92 to ANDA #74-229, reviewed by L.A. Ouderkirk, Division of Bioequivalence).

COMMENT:

Since this study has already been started, the Division of Bioequivalence will make no review of the study protocol at this time, but looks forward to reviewing the completed study upon its submission to the Agency.

RECOMMENDATIONS:

1. The firm should be informed of the above comment.

4-16-93
Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

RD INITIALED ATWU
FT INITIALED ATWU Date: 4/16/93

cc: ANDA 74-229 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-652 (Wu, Ouderkirk), Drug File, Division File

LAO/041593/ntp/041693/WP #74229P.193

NOV 23 1992

Nadolol Tablet USP
20 mg, 40 mg, 80 mg, 120 mg & 160 mg
ANDA # 74-229
Reviewer: Hoainhon Nguyen
WP # 74229P.692

Zenith Laboratories
Northvale, New Jersey
Submission Date:
June 25, 1992

Review of Protocol

Per telephone conversation on November 5th, 1992, between Larry Galvin of Division of Bioequivalence and the firm, it has been confirmed that the study, of which the protocol had been submitted here, was already initiated. Therefore, no review of the protocol by the Division of Bioequivalence is necessary at the present time.

11/19/92

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED ATWU
FT INITIALED ATWU

HNguyen/htn/11-06-92/ntp/111892/WP #74229P.692

cc: ANDA # 74-229 original, HFD-600(Hare), HFD-652(Wu, Nguyen), HFC-130(Allen), Drug File.

SEP 15 1994

Nadolol
Tablets, 20 mg, 40 mg
ANDA #74-229 & 74-255
Reviewer: L.A. Ouderkirk
WP #74229AS.093

Zenith Laboratories, Inc.
Northvale, New Jersey
Submission Date:
October 28, 1993
January 14, 1994

Addendum to a Review of Three Fasted In-Vivo Bioequivalence Studies and One Post-Prandial Bioequivalence Study

The review of the firm's 10/28/93 and 1/14/94 bioequivalence study submissions to ANDA #74-229 is ammended by the addition of the following comments:

Comments:

1. The firm has conducted three fasting in vivo bioequivalence studies on its nadolol tablets, 40 mg. These studies have been found unacceptable by the Division of Bioequivalence.

2. The formulations for the firm's 160 mg, 120 mg, and 80 mg nadolol tablets contains of an inert ingredient, sodium starch glycolate, which the 40 mg and 20 mg tablets do not contain.

3. In consideration of the above comments, the firm should conduct a three-way in vivo food effects study on its 160 mg nadolol tablets versus 160 mg Corgard® tablets, in order to satisfy the bioequivalence and waiver requirements for its 160 mg, 120 mg, and 80 mg nadolol tablets.

The firm should be advised of the above Comments.

Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

RD INITIALED AJJACKSON
FT INITIALED AJJACKSON

Concur: _____ Date: 9/15/94
Rabindra N. Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

DRUG NAME: Nadolol **ANDA #:** 74-229 Not first Generic
SPONSOR: Zenith Laboratories
DOSAGE FORM: Tablet **STRENGTH:** 20mg & 40mg
TYPE OF STUDY: Single dose, fasting.
STUDY SITE:
CLINICAL:
ANALYTICAL:

STUDY SUMMARY:

Fasting: 2-way cross over in 64 subjects. Due to large number of subjects, they were divided into two groups with 32 subjects per group. 59 subjects completed both phases of the study, but five (5) samples of one subject (Subject #29) were destroyed during the transit. Thus total number of evaluable subjects for this study was 58 . 90% C.I. limits on LAUCt (88.0% - 108%), LAUCinf (89.0% - 107%) and LCmax (87.0% - 107%) are within acceptable ranges.

Waiver request for 20 mg tablet: The ***in-vivo*** fasting biostudy on 40 mg tablet is found acceptable and the compositions of 20 mg and 40 mg are exactly proportional. Both 20mg and 40mg tablet strengths meet the dissolution specification of NLT , in 30 minutes. The waiver request for 20 mg tablet is therefore granted.

DISSOLUTION: USP XXII, Basket, 100 RPM
Medium: 0.1N HCl, 900 ml at 37°C.
Specification: NLT of the labeled content is dissolved in 30 min.

PRIMARY REVIEWER: Nhan L. Tran, Ph.D. **BRANCH:** II

INITIAL: _____ DATE: July 29, 1996

TEAM LEADER: Srinivas Nerurkar, Ph.D. **BRANCH:** II

INITIAL: _____ DATE: 7/30/1996

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Keith K. Chan, Ph.D.

INITIAL: _____ DATE: 7/31/96

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: N/A DATE: _____

DBE STUDY APPROVAL FORM

ANDA #:	**74-229**	**FIRM:**	**Zenith**	**FIRST GENERIC:**	**No**
DRUG:	**Nadolol**	**DOSAGE FORM:**	**Tablet**	**STRENGTH:**	**20mg, ~~40mg~~**
RLD:	**Corgard^{R}**	**FIRM:**		**BIO REVIEWER:**	**N. Tran**

Therapeutic Category: Beta-Blocker
Dosage Regimen: Once a day
Solubility/Permeability: High solubility

Clinical Procedure:

Center:
Principal Inv.:
# of Subjects Planned: 64
Extra: No
dropped out: 5
Reasons: Failed to return
# of subject completed: 59
in data analysis: 58 (1 additional subject completing all phases was removed due to 5 samples were destroyed during transit (#29).
Subset analysis: N/A
Randomization: Yes
Demographic: All males, 26 whites, 1 Asian, 37 blacks, age between 19-50
Dose administration: 2x40mg
Blood sample: All collected within 5%of scheduled time, except 6 samples
Safety summary: 46 subjects reported a total of 87 adverse events. The most frequently reported events were decreased pulse in 27 subjects, decreased diastolic blood pressure in 18 subjects. All of the events were mild in severity.

Analytical Procedure:

Center:
Principal Inv.: same
Analytical Method
Pre-study validation:

Stability validation:
Within study validation:
Standard curve:
Comments: Acceptable

PK/Statistical Analysis:

Center:
Investigator: same
PK Calculation Procedure: Trapezoid for AUCs, Cmax from raw data.Spot checked data ok
Mean Plasma Profile: ok
Individual Plasma Profile:checked and ok

Summary of PK Parameters:

	Test	Reference	90% C.I	intra CV	inter CV	Total CV
AUC_{0-t}	2071 ng.ml/hr	2053 ng.ml/hr	88%-108%	30.3%	4%	34.3%
$AUC_{0-\infty}$	2262	2245	89%-107%	28.0%	3.65%	31.65%
C_{max}	181 ng/ml	173 ng/ml	87%-117%	49.8%	6.26%	56.06%

Comments: Parameter calculation and 90% C.I were spot checked and found ok
Statistical Procedure: Appropriate for 2-way cross-over (using group effect in the model).
Comments: All parameters were within the acceptable 90% C.I limits .

In-Vitro Dissolution:

USP Method: USP XXIII Method 1
Specifications: NLT n 30 mi.
Summary dissolution data: USP XXIII Method 1 (basket), 900 ml 0.1N Hcl, 100 PRM

Waiver Request For 20mg Tablet: Granted based on acceptable in-vivo and in-vitro data. In addition, the formulation of 20mg tablet is exactly proportional to 40 mg tablet.

Comparison to Past Generic Products: OK

Approved 7/21/96

JUL 25 1996

Nadolol Tablets, 20 mg, 40 mg
ANDA #74-229
Reviewer: Nhan L. Tran
WP #742290.596

Zenith Laboratories. Inc.
Northvale, New Jersey
Submission Date:
May 2, 1996

REVIEW OF A SUPPLEMENT TO A FASTED IN-VIVO BIOEQUIVALENCE STUDY

I. BACKGROUND

Zenith submitted a study on October 20, 1995 (PROTOCOL FOR STUDY #10880: A SINGLE-DOSE, FASTING, TWO-PERIOD, IN VIVO BIOEQUIVALENCE STUDY IN 64 SUBJECTS). This study was reviewed on March 26, 1996 and was found incomplete.
In the present supplement, the firm is responding to the deficiencies cited by the Agency in the March 26, 1996 review.

II. BRIEF SUMMARY OF THE STUDY

The bioequivalence study was conducted at
The principal investigator was The study was designed as a random, fasted, two-treatment crossover using 64 healthy male subjects, in two groups.

Dosing Group #1: 32 subjects (Subjects #1-#32):
Study Phase 1: July 29 - August 1, 1995, Study Phase 2: August 12 to August 15, 1995.

Dosing Group #2: 32 subjects (Subjects #33-#64):
Study Phase 1: August 11 to August 14, 195, Study Phase 2: August 25 to August 28, 1995

Test (Treatment A): Nadolol Tablets, 2 X 40 mg, (Zenith), Lot # ND-047, Exp. Date: January 1, 1996.

Reference (Treatment B): Corgard^{R} Tablets, 2 X 40 mg, (Princeton/Squibb), Lot # 1A61746, Exp. Date = 1/1/96.

Blood pressure and pulse measurements were taken pre-dose and at 1, 2, 3, 4, 8, 12, 16, and 24 hours post-dose. Venous blood samples (10 ml) were drawn pre-dose (zero hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose. The blood samples were allowed to clot at room

temperature for 30 minutes and were then centrifuged at 10° C. The separated serum was frozen at -20° C. within 24 minutes of centrifugation and stored until assayed. A two-week washout period was observed between the study phases.

Of the 64 subjects enrolled in the study, 59 completed both phases. The participation of subject #1, 27, 30, and 44 was discontinued after completing phase 1. Subject #40 completed both periods but failed to return for the 36, 48, and 60 hours blood draw in period 1. In addition, the samples for subject #29 were not assayed because, according to the firm, five samples were destroyed during transit from the clinic to the laboratory. Thus, the total number of evaluable subjects in this study was 58.

III. REVIEW OF THE SUPPLEMENT: FIRM'S RESPONSES TO THE FDA'S COMMENTS.

1. FDA 1:

Firm's Response:

2. FDA 2:

Firm's Response:

3. FDA 3:

Firm's Response:

4. FDA 4: For subject #29, it is requested the firm should submit complete information concerning the broken samples: sample ID, period, treatment and sampling times at which the samples (broken) were taken.

Firm's Response:
treatment A (test), period 1 were accidentally destroyed during the transit from the clinic to the analytical laboratory. The Sponsor decided not to assay all samples from this subject.
Since all samples from this subject were not assayed, the exclusion of this subject in the statistical analysis was considered unbiased and the response is acceptable.

5. FDA 5: For subject #40, the firm is requested to provide the reasons and complete information for the missing of the 36hrs, 48hrs and 60hrs blood samples of period 1.

Firm's Response: Subject #40 did not provide explanation for not returning as scheduled for 36, 48, and 60 hours of period 1. The Sponsor decided not to assay all his samples, and thus this subject was excluded from statistical analysis. The firm's response is acceptable.

6. FDA 6: Comparative dissolution profiles for the lot used in this study and the one used in previous studies should be submitted for evaluation.

Firm's Response: Since identical tablets were used for all biostudies, no additional dissolution data was generated.
The response is deemed acceptable.

RECOMMENDATIONS:

1. The fasted in vivo bioequivalence study, protocol #10880: A SINGLE-DOSE, FASTING, TWO-PERIOD, IN VIVO BIOEQUIVALENCE STUDY IN 64 SUBJECTS (58 completed) conducted by , on its nadolol tablets, 40 mg, lot #ND-047, versus the listed reference product, Corgard® Tablets, 40 mg, Lot #1A61746, manufactured by Bristol/Squibb, has been found acceptable to the Division of Bioequivalence. Previously, a non-fasting study on 40 mg tablet submitted on May 1993 was found acceptable by the Agency on March 5, 1994.

2. The dissolution testing conducted by Zenith Laboratories on its 20 mg and 40 mg nadolol tablets, Lot # ND 047 for 40 mg, and Lot # ND 048 for 20 mg, versus Corgard® tablets Lot # OA51800 for 20 mg tablet and Lot # 1A61746 for 40 mg tablet is acceptable. Since the biostudies (fasting and fed) on 40 mg tablets as well as dissolution data on 40 mg and 20 mg tablets are acceptable and the formulations of 20 mg tablet is proportionally similar to the 40 mg tablet, the waiver request for 20 mg tablet is granted.

3 The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37°C using USP XXIII Apparatus I (basket) at 100 rpm. The test product should meet the USP specifications:

> Not less thar of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

From the bioequivalence point of view, the firm has met the in-vivo bioequivalence and in-vitro dissolution requirements and the application for nadolol 20mg and 40mg tablets, ANDA 74-229, by Zenith Laboratories is acceptable.

Nhan L. Tran, Ph.D.
Review Branch II

RD INITIALED BY SNERURKAR. 7/18/1996
FT INITIALED BY SNERURKAR.

Concur: ____ Date: 7/25/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-229 (original), HFD-600 (OGD, Hare), HFD-630, HFD-344 (CTViswanathan), HFD-655 (Nerurkar, Tran), Drug File, Division File.

APPENDIX

BACKGROUND INFORMATION:

Nadolol is a long-acting, synthetic, non-selective beta-adrenergic receptor blocker used to treat essential hypertension, cardiac arrhythmia, and angina pectoris. The absorption of nadolol from the G.I. tract is variable following oral dosing, averaging about 30%. About 20-30% of the drug is reversibly bound to plasma proteins. Peak blood serum concentrations are reached within one to four hours following oral administration. The elimination half-life is in the range of 12 to 24 hours, permitting once daily dosing. Because nadolol is excreted unchanged primarily in the urine, its half-life increases in patients with renal impairment. Pharmacokinetically, the drug is described by an open, two-compartment model. The approved labeling for the drug states that the presence of food in the G.I. tract does not affect the rate or extent of absorption and that nadolol may be dosed without regard to meals. The product is marketed as oral tablets in strengths of 20, 40, 80, 120, and 160 mg (Corgard^{R}, Princeton Laboratories/Squibb).

APPROVAL REQUIREMENTS:

The Office of Generic Drugs issued an in vivo bioequivalence and in vitro dissolution guidance for nadolol tablets on 5/16/92. This guidance states that firms seeking approval for nadolol tablets in strengths of 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg should conduct a) a fasted bioequivalence study on the 40 mg strength, b) a fasted bioequivalence study on the 160 mg strength and c) a postprandial study on the 40 mg strength. Provided the strengths are proportionally formulated and meet the dissolution standards, the in vivo bioequivalence requirements for the 20 mg, 80 mg, and 120 mg test product strengths can be waived.

At the present time, Corgard^{R} manufactured by BMS, is available in 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg tablets strengths. Zenith submitted separate applications (ANDA 74-255 for 80 mg, 120 mg and 160 mg strengths, and ANDA 74-229 for 20 mg and 40 mg strengths) for this drug products.

HISTORICAL INFORMATION ON APPROVAL STATUS FOR ZENITH'S APPLICATIONS:

For this application, two ANDAs were submitted:

ANDA #74-255	Nadolol Tablets, 160, 120, 80 mg	Acceptable
ANDA #74-229	Nadolol Tablets, 40, 20 mg	Unacceptable

The Sponsor submitted the following studies to support the application:

	Study	Type	Dose	No. Subj.	EDA Recommendation
1)	10333A	Fasting	2x40 mg	35	Unacceptable
2)	10511	Fasting	2x40 mg	19	Unacceptable
3)	10468	Food	2x40 mg	36	Acceptable
4)	10591	Fasting	4x40 mg	57	Unacceptable
5)	10433	Food	2x40 mg	12	Acceptable
6)	10334A	Fasted	1x160 mg	35	Acceptable

A summary of the studies is as follows:
The firm submitted four in-vivo bioequivalence studies dated 10/28/93 and 1/14/94 to ANDA 74-229 for the 40 mg test product and two studies for 160 mg tablets:
(1) study **#10333A**: A two-way fasted crossover design using a 2 x 40 mg dose.
(2) study **#10511**: A fasted two-treatment, four-period replicate design using a 2 x 40 mg dose. Studies 1033A and 10511 were unacceptable due to C.I Cmax outside acceptable limits.
(3) study **#10468**: A full, two-treatment, two-period, postprandial crossover design using a 2x40 mg dose. This non-fasting study cannot be used in lieu of a fasting study and hence unacceptable.
(4) study **#10591**: A fasted, two-treatment, two-period, crossover study in 58 subjects using a 4 x 40 mg dose. This study was found unacceptable due to the study design unsuitable for 40 mg strength, since for 40 mg strength, a 2x 40 mg tablets should be used, not 4x40 mg tablets.
Subsequently, the firm submitted a bioequivalence study (Study **#10334A**, a two-way fasted crossover design conducted on its 160 mg strength, ANDA 74-255). This fasting study was reviewed by the Division and found acceptable.

The firm submitted (5/6/93) study **#10433**, a single-dose three-way in vivo food effects study conducted on the 40 mg strength of the test product. The study was found acceptable.

COMPARATIVE FORMULATIONS *ZENITH'S NADOLOL TABLETS

(From earlier submission)

COMPONENT	MG/TAB 20 MG TAB	W/W%	MG/TAB 40 MG TAB	W/W%
Nadolol, USP	20.00	13.3	40.00	13.3
Citric Acid, USP				
Green Aluminum Lake Blend**				
Povidone, USP				
Corn Starch, NF				
Microcrystalline Cellulose, NF				
Mag. Stearate, NF				
Totals	150.00	100%	300.00	100%

In Vitro Dissolution Testing For 20 mg and 40 mg Tablets

Drug (Generic Name): Nadolol Tablets
ANDA No.: 74-229 Firm:
Submission Date: 5/6/93
File Name: 74229SDW.593

Dose Strengths: 40 mg, 20 mg
Zenith Laboratories.

I. Conditions for Dissolution Testing:

Apparatus: USP XXIII Basket, RPM: 100
Medium: 0.1N HCL
Tolerance (USP): NLT Q) in 50 minutes
Reference Drug: Corgard[R] Tablets (Princeton)
Assay Methodology: per USP XXII.

No. Units Tested: 12
Volume: 900 mL.

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # ND-048 Strength (mg): 20			Reference Product Lot # OA51800 Strength (mg): 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	59		14.5	45		26.5
15	94		6.3	78		12.0
30	97		2.0	97		1.9
50	97		1.8	99		2.7
60	97		1.7	98		1.0

Sampling Times (Minutes)	Test Product Lot # ND-047 Strength(mg): 40			Reference Product Lot # 1A61746 Strength(mg): 40		
	Mean %	Range	%CV	Mean %	Range	%CV
10	53.4		18.3	45.0		25.6
15	95.0		11.3	89.0		18.6
30	100.9		1.76	99.9		1.38
50	101.3		1.45	101.3		1.02
60	101.5		1.70	102.2		1.82

MAR 5 1994

Nadolol
Tablets, 20 mg, 40 mg
ANDA #74-229
Reviewer: L.A. Ouderkirk
WP #74229SDW.593

Zenith Laboratories, Inc.
Northvale, New Jersey
Submission Date:
May 6, 1993

Review of an In-Vivo Post-Prandial Bioequivalence Study, Dissolution Data and a Waiver Request

BACKGROUND:

Nadolol is a long-acting, synthetic, non-selective beta-adrenergic receptor blocker used to treat essential hypertension, cardiac arrhythmia, and angina pectoris. The absorption of nadolol from the G.I. tract is variable following oral dosing, averaging about 30%. About 20-30% of the drug is reversibly bound to plasma proteins. Peak blood serum concentrations are reached within one to four hours following oral administration. The elimination half-life is in the range of 12 to 24 hours, permitting once daily dosing. Because nadolol is excreted unchanged primarily in the urine, its half-life increases in patients with renal impairment. Pharmacokinetically, the drug is described by an open, two-compartment model. The approved labeling for the drug states that the presence of food in the G.I. tract does not affect the rate or extent of absorption and that nadolol may be dosed without regard to meals. The product is marketed as oral tablets in strengths of 20, 40, 80, 120, and 160 mg (Corgard^{R}, Princeton Laboratories).

SUBMISSION HISTORY:

The firm has previously submitted bioequivalence study #10334A, a two-way fasted crossover design conducted on its 160 mg strength of nadolol tablets, ANDA 74-255. This study, dated November 19, 1992, was reviewed by the Division and found acceptable; however, approval of ANDA 74-255 for nadolol strengths 160 mg, 120 mg, and 80 mg was denied pending demonstration of comparable food effect (versus Corgard^{R}) for either the 160 mg or 40 mg strength. If comparable food effect was to be demonstrated on the 40 mg strength, fasted bioequivalence for the 40 mg tablet would also be required to be demonstrated in order for the 160 mg, 120 mg, and 80 mg strengths to meet the bioequivalence requirements.

Besides the present submission, the firm has submitted three additional in vivo bioequivalence studies to ANDA 74-229, dated 10/28/93, for the 40 mg test product: (1) study #10333A (a two-way fasted crossover design), (2) study #10511 (a fasted two-treatment, four-period crossover design), and (3) study #10468 (a full, two-

way post-prandial crossover design). These studies are currently awaiting review by the Division of Bioequivalence.

PROTOCOL FOR STUDY #037-55-10433: A SINGLE-DOSE POST-PRANDIAL IN-VIVO BIOEQUIVALENCE STUDY:

A. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

The bioequivalence study was conducted at The principal investigator was

B. STUDY OBJECTIVE:

One objective of the study was to determine if the in vivo absorption of the test and reference products was similar when the products were given immediately after a meal. A second objective was to compare the absorption of the test product when dosed under fed versus fasted conditions.

C. STUDY DESIGN:

The study was designed as a random, three-period, three-treatment crossover using 12 healthy male subjects.

D. SUBJECT SELECTION CRITERIA:

Subjects selected for the study met the following acceptance criteria:

1. Aged 19-50 years.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
3. No concurrent illness, acute or chronic diseases or history of asthma, unexplained syncope, myocardial ischemia, prostatic enlargement, bronchitis, rhinitis, diabetes, thyroid disease, or serious cardiovascular, renal, G.I., hepatic, or hematopoietic disease.
4. No history of alcohol or drug abuse.
5. No allergy to nadolol/beta blockers, atropine, epinephrine, or albuterol.
6. No evidence of hypoglycemia.
7. Normal electrocardiogram with no evidence of first degree AV block.
8. Resting B.P. and pulse rate of at least 100/60 mmHg and 55 bpm, respectively.

9. Weight within 15% of ideal for height (Metropolitan Life Insurance Company Bulletin, 1983).

E. SUBJECT RESTRICTIONS:

1. No alcohol consumption beginning 24 hours prior to dosing and lasting until 48 hours after.
2. No concurrent medication of any type.
3. No Rx or OTC drugs beginning two weeks prior to the study.
4. Controlled diet - no xanthines beginning 24 hours before dosing.

F. STUDY SCHEDULES:

Eighteen subjects were fasted for ten hours overnight prior to dosing. The volunteers were randomly numbered and divided into six equal dosing groups in order to balance the dosing sequences, as follows:

	TREATMENT		
Group	Phase 1	Phase 2	Phase 3
1	A	B	C
2	B	C	A
3	C	A	B
4	C	B	A
5	B	A	C
6	A	C	B

In Treatments A and B, below, subjects were given 30 minutes to consume a standard breakfast consisting of one fried egg, one buttered English muffin, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 180 ml of orange juice and 240 ml of whole milk. After an additional 5 minutes, the subjects were administered an 80 mg oral dose (2 x 40 mg tablets) of the test or reference product with 240 ml of water. Subjects receiving the fasted Treatment C were administered an 80 mg dose of the test product with 240 ml of water only. All of the subjects fasted until 5 hours post-dose, when a standard lunch was served. Water *ad lib* was permitted except within one hour of drug administration. Only the food served was permitted for 24 hours after dosing.

Blood pressure and pulse measurements were taken pre-dose and at 1, 2, 3, 4, 8, 12, 16, and 24 hours post-dose. Venous blood samples (10 ml) were drawn pre-dose (0 hours) and at 0.5, 1, 1.5,

2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose. The blood samples were allowed to clot at room temperature for 30 minutes and were then centrifuged at 10^0 C. The separated serum was frozen at -20^0 C. within 24 minutes of centrifugation and stored until assayed. A two-week washout period was observed between Phase 1 and 2 dosing.

G. DRUG TREATMENTS:

1. Test Treatment A (Fed): Nadolol Tablets, 2 X 40 mg, (Zenith), Lot # ND-047, Assayed Potency (n=30) = 101.0%, Exp. Date = 7/15/93 Lot Size = units (ref. Vol. 3, p.807)

2. Reference Treatment B (Fed): Corgard^R Tablets, 2 X 40 mg, (Princeton), Lot # 1A61746, Assayed Potency (n=10) = 99.1%, Exp. Date = 1/1/96

3. Test Treatment C (Fasted): Nadolol Tablets, 2 X 40 mg, (Zenith), Lot # ND-047

H. CLINICAL NOTES:

Twelve of the 18 subjects completed the study; six did not. The participation of subjects #7, #10, and #18 was discontinued for medical reasons judged to be unrelated to the study medications. Subjects #4 and #12 failed to return to the study site to complete the study. Subject #11 was dropped from the study due to positive urine drug screen results. The following schedule was observed:

Study Phase 1: October 21 - 25, 1992; Dosing date = 10/21/92
Study Phase 2: November 4 - 8, 1992; Dosing date = 11/5/92
Study Phase 3: November 18 - 22, 1992; Dosing date = 11/19/92

Nineteen adverse events were reported by a total of 12 subjects (Table 1). Six adverse events were recorded for the test product and 13 for the reference; all were judged mild in severity. Five of the events were judged probably related to the study drug, 5 possibly related, and 9 unrelated.

I. ASSAY METHOD PERFORMANCE AND VALIDATION STUDY:

K. STATISTICAL ANALYSIS:

The study data for 12 subjects were analyzed by ANOVA and the F-test to determine statistically significant (α=0.05) differences between treatments, dosing sequence, subjects within sequence, and days of administration for areas under the curve (AUC), maximum serum drug levels (Cmax), time to maximum drug levels (Tmax), elimination constants (Kel) and half-life values (T 1/2). ANOVA was performed for subject serum drug concentrations at each sampling time and included all sums of squares (Types I-IV).

The 90% confidence intervals (two, one-sided tests procedure) were also calculated for the AUC and Cmax parameters. The statistical analysis was performed using SAS^R version 6.07 and PROC GLM for the ANOVA. Since statistical evaluation of the 90% confidence intervals for limited food-effect studies is not required for bioequivalence determination, these data are not discussed in this review.

L. INFORMED CONSENT AND IRB APPROVAL:

Subjects gave written, informed consent prior to their acceptance into the study. The study protocol was reviewed and approved by an IRB prior to its initiation.

PHARMACODYNAMIC MEASUREMENTS:

The firm statistically analyzed the blood pressure and pulse measurement data obtained post-dose, although the study was not primarily designed to measure any pharmacological effects or relate such effects to serum drug concentration.

Mean systolic blood pressure decreased significantly at 3, 4 (maximum decrease of 15.3 mmHg), 8, and 12 hours after the (non-fasting) Zenith treatment dose, at 2, 3, 4 (maximum decrease 18.4 mmHg), 8, 16, and 24 hours after the (non-fasting) Corgard^R reference formulation was given and at 2, 3, 4 (maximum decrease 15.4 mmHg), and 24 hours after the Zenith treatment dosed under fasted conditions.

Mean diasystolic blood pressure decreased significantly from 2 to 24 hours after administration of the fed test treatment, 1 to

12 hours after the Corgard[R] reference dosed fed and at 2 and 12 hours after administration of the reference formulation under fasted conditions. The linearity of mean changes in systolic blood pressure versus concentration revealed clockwise hysteresis for both the test and reference treatments dosed after a meal. Plots of mean change in diastolic blood pressure versus concentration were not linear. A linear fit of effect versus nadolol concentration was not attempted.

RESULTS OF BIOEQUIVALENCE STUDY:

The results of the food effects study for 12 subjects are summarized in Tables 2 - 3 and Figure 1. When dosed following the standard breakfast, the mean AUC(0-t) and Cmax for the test versus the reference products differed by only 1%. The test formulation dosed following the standard breakfast was absorbed more slowly and to a lesser extent than when dosed under fasted conditions. When the test product was dosed following a meal, the mean AUC(0-t) was lowered by 26%, the AUC(Inf) was lowered by 23% and mean Cmax was lowered by 33% compared to the test product dosed fasted.

IN-VITRO DISSOLUTION TESTING RESULTS:

The firm conducted dissolution testing on its 40 mg and 20 mg strengths of the test product versus the reference product, Corgard[R] Tablets, manufactured by Princeton Laboratories. The testing was conducted according to the method specified in USP XXII for this product. The results of the dissolution testing and a description of the method are given in Table 4.

REQUEST FOR WAIVER OF IN-VIVO BIOEQUIVALENCE:

The firm has requested waiver of the in-vivo bioequivalence study requirements for its 20 mg strength of the test product, based on an acceptable in-vivo bioequivalence study on the 40 mg strength, comparative dissolution data (Table 4) and proportional formulations (Table 5).

COMMENTS:

1. The test product exhibited a significant reduction in both the rate and extent of absorption when dosed under post-prandial conditions. The labeling for Corgard[R] tablets states that the presence of food in the gastrointestinal tract does not affect the rate or extent of absorption and that the product may be dosed without regard to meals. It is recommended that these findings be referred to the OGD Labeling Review Branch for their consideration

in the review of the product labeling.

2. The firm has demonstrated a similar effect of food on drug absorption for its 40 mg test product compared to Corgard^{R} 40 mg tablets. However, as a condition of product approval, bioequivalence of the 40 mg test product must also be demonstrated under fasting conditions.

3. Waiver of the in-vivo bioequivalence requirements for the 20 mg strength of the test product per 21 CFR 320.22 (d) (2) cannot be granted pending approval of the 40 mg test product strength.

4. An apparent discrepancy in the lot number listed for the 40 mg Corgard^{R} reference product in Section 3 of the submission was confirmed as a typographical error by Jean F. Cummiskey, Ph.D., Associate Director for Regulatory Affairs, Zenith Laboratories, Inc. In a telecommunication on 2/7/94, Dr. Cummisky confirmed that the correct lot number was 1A61746.

RECOMMENDATIONS:

1. The in vivo food effect study #037-55-10433, conducted under post-prandial conditions by Zenith Laboratories, Inc., on its nadolol tablets, 40 mg, lot #ND-047, versus the listed reference product, Corgard^{R} Tablets, 40 mg, Lot #1A61746, manufactured by Princeton Laboratories, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the in vivo absorption of Zenith's nadolol tablets, 40 mg, is similar to that of the listed reference product, Corgard^{R} Tablets, 40 mg, when dosed immediately following a standard meal. The firm, however, is also required to demonstrate the in vivo bioequivalence of the test product under fasting conditions as a requirement of product approval.

2. The dissolution testing conducted by the firm on its nadolol tablets, 40 mg, lot #ND-047 and 20 mg, lot #ND-048, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml 0.1 N HCL at 37^{0}C using USP XXII apparatus 1 at 100 rpm. The test product should meet the following specifications per USP XXII:

> Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 50 minutes.

3. Waiver of the in-vivo bioequivalence study requirements for the firm's 20 mg test product is denied pending approval of the

firm's 40 mg test product.

4. From the Bioequivalence viewpoint, the firm has not met the in vivo bioequivalence requirements and the ANDA 74-229 is incomplete.

The firm should be advised of the Comments and Recommendations, above.

U 2-24-94

Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

RD INITIALED ATWU
FT INITIALED ATWU U 2/28/94

Concur: _____ Date: 3/5/94
Shrikant V. Dighe, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-229 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CVishwanathan), HFD-652 (Wu, Ouderkirk), Drug File, Division File

LAO/022294/ntp/WP #74229SDW.593

TABLE 1: ADVERSE EVENTS
NADOLOL TABLETS
#037-55-10433

SUBJECT #	TREATMENT	EVENT	SEVERITY	ONSET DATE	ONSET TIME	RESOLUTION DATE	RESOLUTION TIME	RX	RELATION TO DRUG PRODUCT
1	PRINCETON	HOARSENESS	MILD	11/17/92	UNK.	CONTINUES		NONE	UNLIKELY
2	ZENITH(FAST)	SLEEPY	MILD	11/19/92	0915	11/19/92	1000	NONE	POSSIBLE
3	ZENITH(FAST) (predose ph II)	TIRED	MILD	11/05/92	0600	11/05/92	1300	NONE	UNLIKELY
4	PRINCETON	HEADACHE	MILD	10/22/92	1030	10/22/92	1130	NONE	PROBABLE
5	ZENITH(FAST)	INTERMITTENT BLURRED VISION	MILD	10/28/92	UNK.	11/04/92	UNK.	NONE	UNLIKELY
	ZENITH(FED)	UPSET STOMACH		11/05/92	1100	11/05/92	1130	NONE	POSSIBLE
	PRINCETON	"TWITCHING" ON LEFT SIDE OF NECK		11/19/92	1000, 1700, 1850	11/19/92	1015, 1708, 1900	NONE	UNLIKELY
8	ZENITH(FED)	TOOTH FELL OUT	MILD	11/19/92	2045	11/19/92	2050	NONE	UNLIKELY
10	PRINCETON	CHEST & BACK PAINS	MILD	10/22/92	0950	10/22/92	1005	12-LEAD ECG UNCHANGED FROM SCREENING	UNLIKELY
12	ZENITH(FAST)	LIGHTHEADED	MILD	10/22/92	0945	10/22/92	0955	NONE	PROBABLE

UNK. = UNKNOWN

TABLE 1: ADVERSE EVENTS
NADOLOL TABLETS
#037-55-10433

SUBJECT #	TREATMENT	EVENT	SEVERITY	ONSET DATE	ONSET TIME	RESOLUTION DATE	RESOLUTION TIME	RX	RELATION TO DRUG PRODUCT
14	PRINCETON	LIGHTHEADED	MILD	10/22/92	0910	10/22/92	1016	NONE	PROBABLE
	ZENITH(FAST)	STRAINED RIGHT LEG	MILD	11/13/92	UNK.	11/18/92	UNK.	NONE	UNLIKELY
15	ZENITH(FAST)	LIGHTHEADED	MILD	10/22/92	0910	10/22/92	1020	NONE	PROBABLE
	ZENITH(FED)	SLEEPY	MILD	11/05/92	0950	11/05/92	1115	NONE	POSSIBLE
16	PRINCETON	LIGHTHEADED	MILD	10/22/92	0915	10/22/92	1026	NONE	PROBABLE
	ZENITH(FED)	DROWSY	MILD	11/05/92	0930	11/05/92	1110	NONE	POSSIBLE
	ZENITH(FAST)	SLEEPY	MILD	11/19/92	1000	11/19/92	1200	NONE	POSSIBLE
18	ZENITH(FAST)	SLEEPY	MILD	10/23/92	UNK.	10/24/92	UNK.	NONE	UNLIKELY
	ZENITH(FAST)	HEADACHE (predose ph II)	MILD	11/05/92	0800	11/05/92	1000	NONE	UNLIKELY

UNK. = UNKNOWN

TABLE 1: NADOLOL SERUM CONCENTRATIONS (ng/ml)
ARITHMETIC MEANS ± STANDARD DEVIATION (N = 58)
#037-75-10880

Time (Hours)	Zenith Test Product	Bristol-Myers Squibb Reference Product	Ratio Test/Reference	Significance
0	0.0000	0.0000	--	-
0.5	27.34 ± 16.63	20.96 ± 13.48	1.30	$p<0.05$
1	76.14 ± 62.79	62.70 ± 32.35	1.21	N.S.
1.5	94.88 ± 78.55	82.01 ± 55.23	1.16	N.S.
2	102.9 ± 79.97	99.08 ± 69.73	1.04	N.S.
2.5	108.4 ± 74.09	118.3 ± 81.62	0.92	N.S.
3	120.1 ± 85.28	128.9 ± 93.55	0.93	N.S.
3.5	134.6 ± 98.95	132.3 ± 91.51	1.02	N.S.
4	130.8 ± 88.53	126.3 ± 82.87	1.04	N.S.
5	117.3 ± 70.49	117.3 ± 72.93	1.00	N.S.
6	98.02 ± 53.07	98.44 ± 51.31	1.00	N.S.
8	81.48 ± 48.26	77.69 ± 34.96	1.05	N.S.
12	56.28 ± 26.68	55.88 ± 22.97	1.01	N.S.
16	44.36 ± 20.38	43.92 ± 17.48	1.01	N.S.
24	31.64 ± 13.17	31.90 ± 11.95	0.99	N.S.
36	17.15 ± 7.777	17.61 ± 6.226	0.97	N.S.
48	9.229 ± 6.001	9.969 ± 4.573	0.93	N.S.
60	5.096 ± 4.759	4.698 ± 4.374	1.08	N.S.

TABLE 3: PHARMACOKINETIC PARAMETERS
LEAST SQUARES MEANS ± STANDARD ERROR (N = 58)
SERUM NADOLOL
#037-75-10880

Parameter	Test Zenith	Reference Bristol-Myers Squibb	Test/ Reference	Significance	Study Power	Intrasubject C.V.(%)	90% Confidence Interval
AUC 0 t (ng ml⁻¹hr)	2071 ± 81.58	2053 ± 81.58	1.01	N.S.	0.94	30.3	0.91; 1.10
Ln AUC 0 t (Antiln)	7.5138 ± 0.0430 (1833)	7.5419 ± 0.0430 (1885)	0.97	N.S.	0.90	33.6	0.88; 1.08
AUC 0 Inf (ng ml⁻¹hr)	2262 ± 82.59	2245 ± 82.59	1.01	N.S.	0.96	28.0	0.92; 1.09
Ln AUC 0 Inf (Antiln)	7.6205 ± 0.0384 (2040)	7.6454 ± 0.0384 (2091)	0.98	N.S.	0.95	29.9	0.89; 1.07
Cmax (ng/ml)	181.0 ± 11.33	173.1 ± 11.33	1.05	N.S.	0.56	49.8	0.89; 1.20
Ln Cmax (Antiln)	5.0006 ± 0.0627 (148.5)	4.9909 ± 0.0627 (147.1)	1.01	N.S.	0.60	50.6	0.87; 1.17
Tmax (hr)	3.292 ± 0.1444	3.137 ± 0.1444	1.05	N.S.	0.85	35.1	0.94; 1.16
Rate Constant (hr⁻¹)	0.04722 ± 0.00074	0.04617 ± 0.00074	1.02	N.S.	>0.99	12.2	0.99; 1.06
Half Life (hr)	15.79 ± 0.3888	16.07 ± 0.3888	0.98	N.S.	>0.99	18.4	0.93; 1.04
Cmax/ AUCI	0.07691 ± 0.00271	0.07422 ± 0.00271	1.04	N.S.	0.97	27.8	0.95; 1.12
Ln (Cmax/AUCI) (Antiln)	-2.6199 ± 0.0345 (0.07281)	-2.6546 ± 0.0345 (0.07033)	1.04	N.S.	0.98	26.7	0.95; 1.12

The test of equality of the means, the power of the study to detect a 20% difference in parameters as statistically significant (α=0.05), and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means from the analysis of variance.

TABLE 2: PHARMACOKINETIC PARAMETERS
ARITHMETIC MEANS ± STANDARD DEVIATION (N = 58)
SERUM NADOLOL
#037-75-10880

Parameter	N	Test: Zenith Mean ± Std. Dev.	C.V.	N	Reference: Bristol-Myers Squibb Mean ± Std. Dev.	C.V.	Test/ Reference
AUC 0-t (ng ml⁻¹hr)	58	2075 ± 995.7	48.0	58	2056 ± 876.9	42.6	1.01
Ln AUC 0-t Geometric Mean	58	7.5155 ± 0.5171 1836		58	7.5437 ± 0.4186 1889		0.97
AUC 0-Inf (ng ml⁻¹hr)	58	2266 ± 1026	45.3	58	2249 ± 876.0	39.0	1.01
Ln AUC 0-Inf Geometric Mean	58	7.6221 ± 0.4710 2043		58	7.6470 ± 0.3824 2094		0.98
Cmax (ng/ml)	58	181.1 ± 114.7	63.4	58	173.2 ± 103.0	59.5	1.05
Ln Cmax Geometric Mean	58	5.0015 ± 0.6513 148.6		58	4.9917 ± 0.5737 147.2		1.01
Tmax (hr)	58	3.293 ± 1.424	43.2	58	3.138 ± 1.217	38.8	1.05
Rate Constant (hr⁻¹)	58	0.04722 ± 0.01052	22.3	58	0.04617 ± 0.01063	23.0	1.02
Half Life (hr)	58	15.79 ± 5.648	35.8	58	16.06 ± 5.059	31.5	0.98
Cmax/ AUCI	58	0.07683 ± 0.02646	34.4	58	0.07413 ± 0.02443	33.0	1.04
Ln (Cmax/AUCI) Geometric Mean	58	-2.6206 ± 0.3371 0.07276		58	-2.6553 ± 0.3331 0.07028		1.04

Figure 1: Mean Nadolol Serum Levels

#037 – 75 – 10880

N = 58

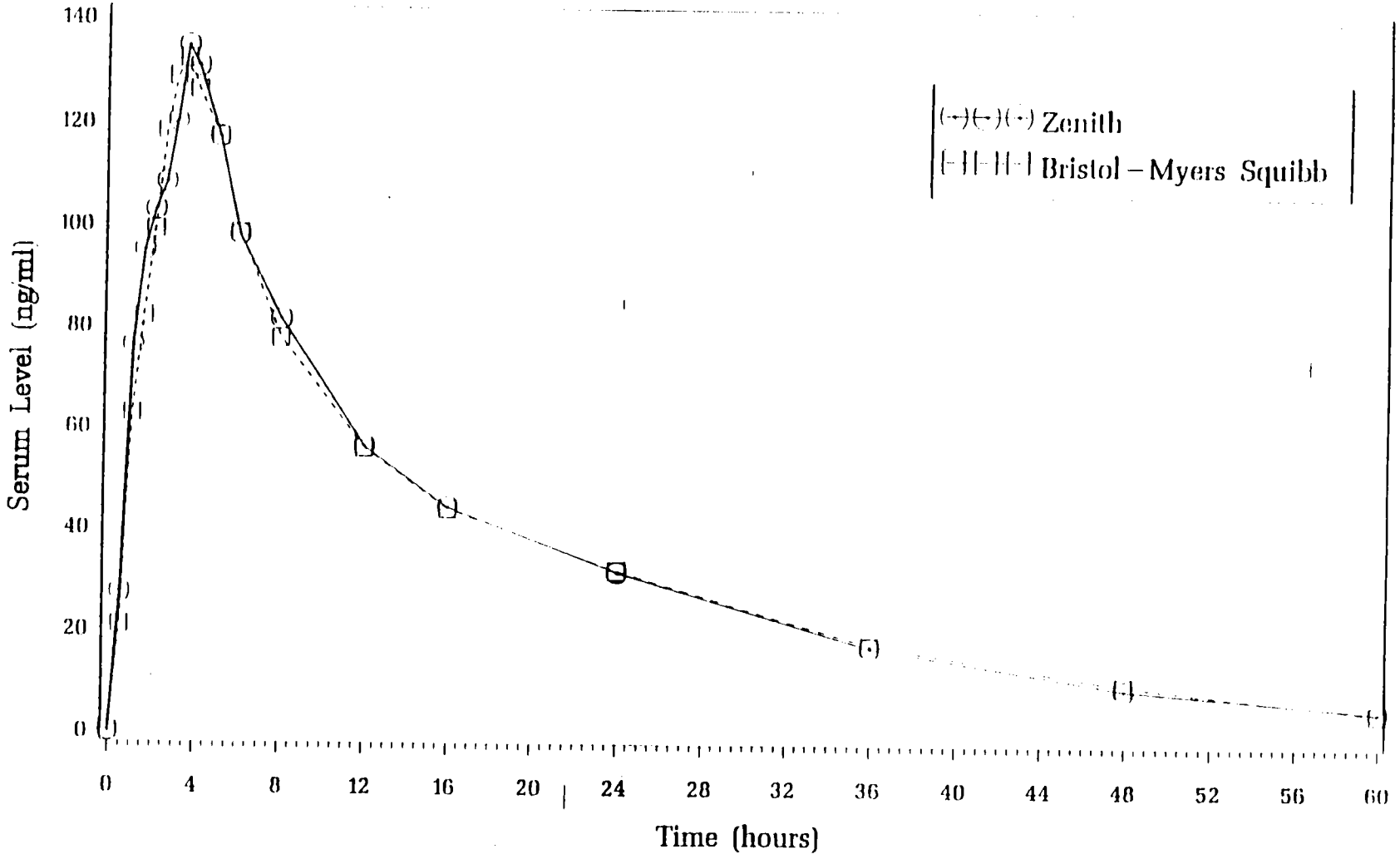


FIGURE 1

Mean Nadolol Serum Levels

n = 12

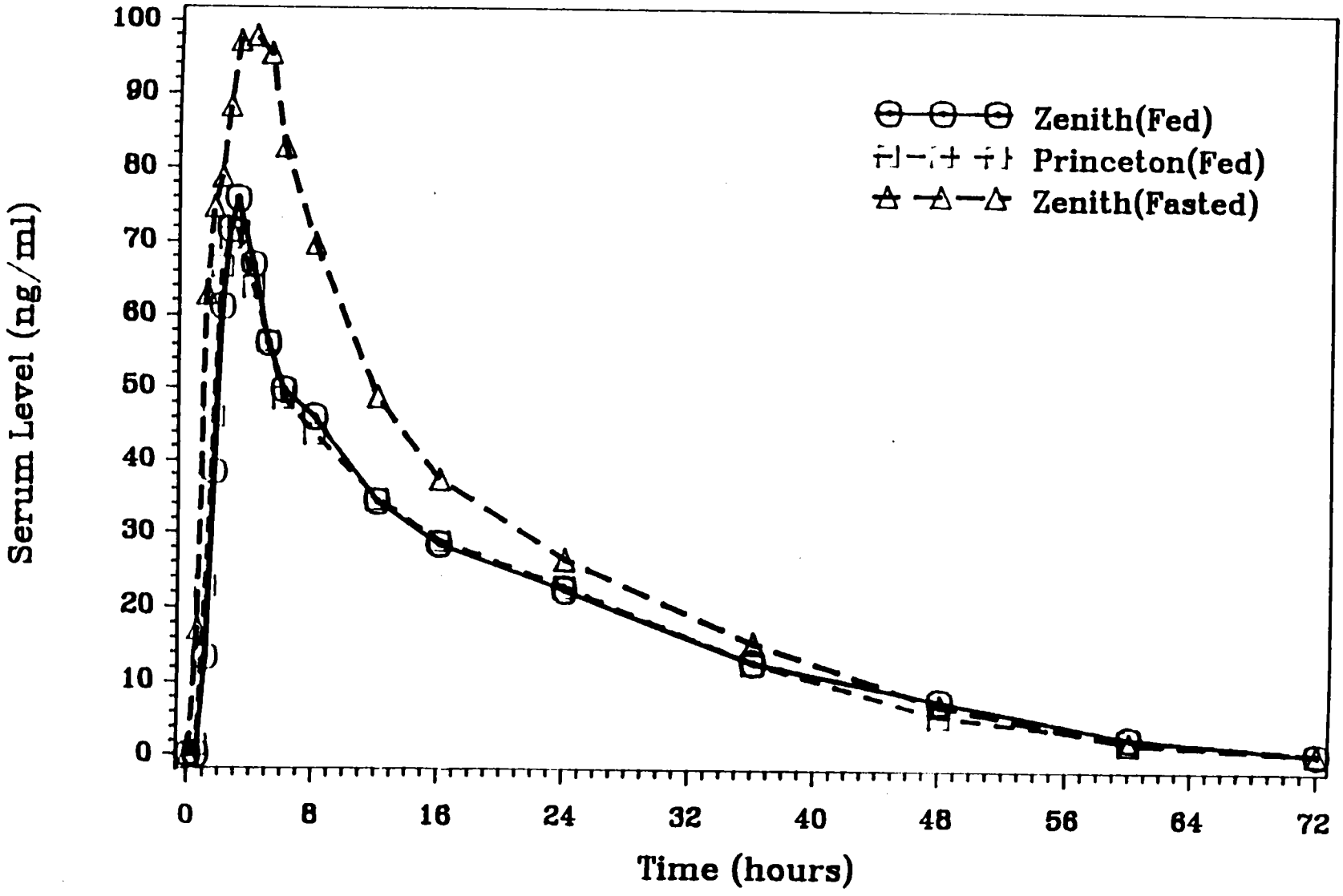


TABLE 2

MEAN NADOLOL POST-PRANDIAL SERUM CONCENTRATIONS (NG/ML)
POST-PRANDIAL STUDY NO. 037-55-10433
N=12 SUBJECTS

Hours	Princet. 40 mg Test A (Fed)	Corgard® 40 mg Ref. B (Fed)	Princet. 40 mg Test C (Fast)	A/B	A/C
0	0.0	0.0	0.0	---	---
0.5	0.0	1.3 (346)*	16.9 (83)	0.0	0.0
1	13.1 (83)	22.6 (101)	62.6 (44)	0.58	0.21
1.5	38.2 (60)	45.9 (61)	74.4 (50)	0.83	0.51
2	60.9 (43)	66.4 (47)	78.5 (44)	0.92	0.78
2.5	71.3 (36)	70.3 (40)	88.1 (48)	1.01	0.81
3	75.5 (39)	71.1 (36)	96.9 (55)	1.06	0.78
4	66.7 (40)	63.6 (40)	97.6 (50)	1.05	0.68
5	55.9 (41)	56.3 (36)	95.2 (49)	0.99	0.59
6	49.4 (37)	48.4 (35)	82.6 (46)	1.02	0.60
8	45.8 (36)	43.6 (29)	69.5 (46)	1.05	0.66
12	34.1 (29)	34.5 (30)	48.5 (41)	0.99	0.70
16	28.2 (31)	28.7 (29)	37.0 (35)	0.98	0.76
24	22.1 (31)	22.6 (29)	26.2 (33)	0.98	0.84
36	12.5 (37)	12.5 (45)	15.2 (40)	1.00	0.82
48	7.5 (59)	5.5 (99)	6.8 (73)	1.36	1.10
60	2.6 (147)	2.5 (154)	1.8 (193)	1.04	1.39
72	0.50 (346)	0.68 (346)	0.55 (346)	0.74	0.91

* (C.V.%)

TABLE 3
POST-PRANDIAL STUDY #037-55-10433
ARITHMETIC MEAN PHARMACOKINETIC PARAMETER VALUES (C.V.%)
N=12 SUBJECTS

Parameter	Treatment A (Test Fed)	Treatment B (Ref. Fed)	Treatment C (Test Fasted)	A/B	A/C
AUC(0-T) [ng/ml x hr]	1240 (34)	1226 (37)	1680 (41)	1.01	0.74
AUC(0-∞) [ng/ml x hr]	1424 (30)	1393 (34)	1854 (37)	1.02	0.77
Cmax [ng/ml]	78.0 (36)	77.5 (38)	117 (43)	1.01	0.67
Tmax [Hrs.]	2.92 (19)	2.83 (24)	3.63 (49)		
T1/2 [Hrs.]	17.7 (21)	16.2 (28)	14.8 (19)		
Kel [Hr^{-1}]	0.0408 (22)	0.0461 (31)	0.0483 (18)		

Table 4 - In Vitro Dissolution Testing

Drug (Generic Name): Nadolol Tablets
Dose Strengths: 40 mg, 20 mg
ANDA No.: 74-229
Firm: Zenith Laboratories, Inc.
Submission Date: 5/6/93
File Name: 74229SDW.593

I. Conditions for Dissolution Testing:

Apparatus: USP XXII Basket
RPM: 100
No. Units Tested: 12
Medium: 0.1N HCL
Volume: 900 mL
Tolerance (USP): NLT (Q) in 50 minutes
Reference Drug: Corgard® Tablets (Princeton)
Assay Methodology: per USP XXII

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # ND-048 Strength (mg): 20			Reference Product Lot # OA51800 Strength (mg): 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	59		14.5	45		26.5
15	94		6.3	78		12.0
30	97		2.0	97		1.9
50	97		1.8	99		2.7
60	97		1.7	98		1.0

Sampling Times (Minutes)	Test Product Lot # ND-047 Strength(mg): 40			Reference Product Lot # 1A61746 Strength(mg): 40		
	Mean %	Range	%CV	Mean %	Range	%CV
10	53.4		18.3	45.0		25.6
15	95.0		11.3	89.0		18.6
30	100.9		1.76	99.9		1.38
50	101.3		1.45	101.3		1.02
60	101.5		1.70	102.2		1.82

TABLE 5 - COMPARATIVE FORMULATIONS*
ZENITH NADOLOL TABLETS

COMPONENT	20 MG TAB		40 MG TAB	
	MG/TAB	W/W%	MG/TAB	W/W%
Nadolol, USP	20.00	13.3	40.00	13.3
Citric Acid, USP				
Green Aluminum Lake Blend**				
Povidone, USP				
Corn Starch, NF				
Microcrystalline Cellulose, NF				
Mag. Stearate, NF				
Totals	150.00	100%	300.00	100%

MAR 26 1996

Nadolol Tablets, 20 mg, 40 mg
ANDA #74-229
Reviewer: Nhan L. Tran
WP #74229S.O95

Zenith Laboratories. Inc.
Northvale, New Jersey
Submission Date:
October 20, 1995

Review of A Fasted In-Vivo Bioequivalence Study

APPROVAL REQUIREMENTS:

The Office of Generic Drugs issued an in vivo bioequivalence and in vitro dissolution guidance for nadolol tablets on 5/16/92. This guidance states that firms seeking approval for nadolol tablets in strengths of 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg should conduct a) a fasted bioequivalence study on the 40 mg strength, b) a fasted bioequivalence study on the 160 mg strength and c) a post-prandial study on the 40 mg strength.
Provided the strengths are proportionally formulated and meet the dissolution standards, the in vivo bioequivalence requirements for the 20 mg, 80 mg, and 120 mg test product strengths can be waived.

At the present time, Nadolol[R] manufactured by BMS, is available in 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg tablets. Zenith submitted separate application (ANDA 74-255) for 80 mg, 120 mg and 160 mg strengths. The present submission (ANDA 74-229) is strictly for 20 mg and 40 mg strengths.

HISTORICAL INFORMATION ON APPROVAL STATUS FOR ZENITH'S APPLICATIONS:

For this application, two ANDAs were submitted:

ANDA #74-255	Nadolol Tablets, 160, 120, 80 mg	Acceptable
ANDA #74-229	Nadolol Tablets, 40, 20 mg	Unacceptable

The Sponsor submitted the following studies to support the application:

	Study	Type	Dose	No. Subj.	FDA Recommendation
1)	10333A	Fasting	2x40 mg	35	Unacceptable
2)	10511	Fasting	2x40 mg	19	Unacceptable
3)	10468	Food	2x40 mg	36	Acceptable
4)	10591	Fasting	4x40 mg	57	Unacceptable
5)	10433	Food	2x40 mg	12	Acceptable
6)	10334A	Fasted	1x160 mg	35	Acceptable

A summary of the studies is as follows:
The firm submitted four in-vivo bioequivalence studies dated 10/28/93 and 1/14/94 to ANDA 74-229 for the 40 mg test product and two study for 160 mg tablets:

(1) study **#10333A**: A two-way fasted crossover design using a 2 x 40 mg dose.

(2) study **#10511**: A fasted two-treatment, four-period replicate design using a 2 x 40 mg dose. Studies 1033A and 10511 were unacceptable due to C.I Cmax outside acceptable limits.

(3) study **#10468**: A full, two-treatment, two-period, post-prandial crossover design using a 2x40 mg dose. This non-fasting study cannot be used in lieu of a fasting study and hence unacceptable.

(4) study **#10591**: A fasted, two-treatment, two-period, crossover study in 58 subjects using a 4 x 40 mg dose. This study was found unacceptable due to the study design unsuitable for 40 mg strength, since for 40 mg strength, a 2x 40 mg tablets should be used, not 4x40 mg tablets.

Subsequently, the firm submitted a bioequivalence study (Study **#10334A**, a two-way fasted crossover design conducted on its 160 mg strength, ANDA 74-255). This fasting study was reviewed by the Division and found acceptable.

The firm submitted (5/6/93) study **#10433**, a single-dose three-way in vivo food effects study conducted on the 40 mg strength of the test product. The study was found acceptable.

However, the application was not approved pending conduct of a fasted bioequivalence study for 40 mg strength, since fasted bioequivalence for the 40 mg tablet would be required, in order for the 160 mg, 120 mg, 80 mg and 40 mg strengths to meet the bioequivalence requirements.

BACKGROUND INFORMATION:

Nadolol is a long-acting, synthetic, non-selective beta-adrenergic receptor blocker used to treat essential hypertension, cardiac arrhythmia, and angina pectoris. The absorption of nadolol from the G.I. tract is variable following oral dosing, averaging about 30%. About 20-30% of the drug is reversibly bound to plasma proteins. Peak blood serum concentrations are reached within one to four hours following oral administration. The elimination half-life is in the range of 12 to 24 hours, permitting once daily dosing. Because nadolol is excreted unchanged primarily in the urine, its half-life increases in patients with renal impairment. Pharmacokinetically, the drug is described by an open, two-compartment model. The approved labeling for the drug states that the presence of food in the G.I. tract does not affect the rate or extent of absorption and that nadolol may be dosed without regard to meals. The product is marketed as oral tablets in strengths of 20, 40, 80, 120, and 160 mg (Corgard^{R}, Princeton Laboratories/Squibb).

PROTOCOL FOR STUDY #10880:
A SINGLE-DOSE, FASTING, TWO-PERIOD, IN VIVO BIOEQUIVALENCE STUDY IN 64 SUBJECTS.

A. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

The bioequivalence study was conducted at
The principal investigator was

B. STUDY OBJECTIVE:

The objective of the study was to compare the rate and extent of absorption of the test, 40 mg tablet versus the reference product under fasting conditions.

C. STUDY DESIGN:

The study was designed as a random, fasted, two-treatment crossover using two dosing groups of 64 healthy male subjects.

Dosing Group #1: 32 subjects (Subjects #1-#32):

Study Phase 1: July 29 - August 1, 1995
Study Phase 2: August 12 to August 15, 1995.

Dosing Group #2: 32 subjects (Subjects #33-#64):

Study Phase 1: August 11 to August 14, 195
Study Phase 2: August 25 to August 28, 1995

D. SUBJECT SELECTION CRITERIA:

Subjects selected for the study met the following acceptance criteria: Aged 19-50 years, healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
No concurrent illness, acute or chronic diseases or history of asthma, unexplained syncope, myocardial ischemia, prostatic enlargement, bronchitis, rhinitis, diabetes, thyroid disease, or serious cardiovascular, renal, G.I., hepatic, hematopoietic disease. No history of alcohol or drug abuse, no allergy to nadolol/beta blockers, atropine, epinephrine, or albuterol, nor evidence of hypoglycemia. Normal electrocardiogram with no evidence of first degree AV block, resting B.P. and pulse rate of at least 100/60 mmHg and 55 bpm, respectively. Weight within 15% of ideal for height (Metropolitan Life Insurance Company Bulletin, 1983).

E. SUBJECT RESTRICTIONS:

No alcohol consumption beginning 24 hours prior to dosing and lasting until 48 hours after, no concurrent medication of any type, nor Rx or OTC drugs beginning two weeks prior to the study, no xanthines beginning 24 hours before dosing.

F. STUDY SCHEDULES:

Subjects were fasted for ten hours overnight prior to dosing. The volunteers were randomly numbered and divided into two dosing groups of equal number. An 80 mg (2x40 mg tablets) oral dose of the test product was administered with 240 ml of water in order of subject number. All of the subjects fasted until 5 hours post-dose, when a standard lunch was served. Water *ad lib* was permitted except within one hour of drug administration. Only the food served was permitted for 24 hours after dosing. Subjects were prohibited from smoking beginning 1 hour before dosing and lasting until 4 hours after dosing.

Blood pressure and pulse measurements were taken pre-dose and at 1, 2, 3, 4, 8, 12, 16, and 24 hours post-dose. Venous blood samples (10 ml) were drawn pre-dose (0 hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose. The blood samples were allowed to clot at room temperature for 30 minutes and were then centrifuged at 10^0 C. The separated serum was frozen at -20^0 C. within 24 minutes of centrifugation and stored until assayed. A two-week washout period was observed between study Phases.

G. DRUG TREATMENTS:

1.Test Treatment A: Nadolol Tablets, 2 X 40 mg, (Zenith), Lot # ND-047, Exp. Date: January 1, 1996. The Sponsor refers other information such as potency, lot size to the original submission. Although lot number was the same as in the previous submission, expiration date was different (07-15-1993). Explanation should be given to demonstrate that no change in the formulation has been made for the new lot.

2.Reference Treatment B: Corgard^R Tablets, 2 X 40 mg, (Princeton/Squibb), Lot # 1A61746, Exp. Date = 1/1/96. The same lot number and expiration date as in the previous submission.

Note: In the previous submission, the following information was reported: For the test formulation: Assayed Potency (n=30) = 101.0%, Exp. Date = 7/15/93, Lot Size = nits, and for the reference formulation: Lot # 1A61746, Assayed Potency (n=10) = 99.1%, Exp. Date = 1/1/96.

H. CLINICAL NOTES:

Of the 64 subjects enrolled in the study, 59 completed both phases. The participation of subject #1, 27, 30, and 44 was discontinued after completing phase 1. Subject #40 completed both periods but failed to return for the 36, 48 and 60 hour blood draw in period 1. In addition, samples for subject #29 were not assayed because, according to the firm, 5 samples were destroyed during transit from the clinic to the laboratory. Thus, the total number of evaluable subjects in this study was 58.

Eighty eight adverse events were reported by a total of 46 subjects. 47 and 41 adverse events were recorded for the test and reference products respectively; all were judged mild in severity.

J. ASSAY METHOD PERFORMANCE AND VALIDATION STUDY:

K. STATISTICAL ANALYSIS:

The 90% confidence intervals (two one-sided tests procedure) were calculated for the AUC and Cmax parameters. The statistical analysis was performed using SAS® and PROC GLM for the ANOVA.

L. INFORMED CONSENT AND IRB APPROVAL:

Subjects gave written, informed consent prior to their acceptance into the study. The study protocol was reviewed and approved by an IRB prior to its initiation.

M. RESULTS OF BIOEQUIVALENCE STUDY #10880:

1. ANALYTICAL:

2. PHARMACOKINETIC AND STATISTICAL ANALYSES:

Because of the relatively large number of subjects who participated in this study, the volunteers were divided into two separate groups who were dosed at different times. Consequently, the statistical analysis for this study included a sequence-by-group factor to determine if there were any effects of dosing group on the study results.

The results of the bioequivalence study for 58 subjects are summarized in Tables below. The 90% confidence intervals reported by the firm for the test versus the reference products were 88% - 108% for LnAUC(0-t) and 89% - 107% for LnAUC(inf), and 87% - 117% for LnCmax.

N. DEFICIENCIES:

4. For subject #29, it is requested the firm should submit complete information concerning the broken samples: sample ID, period, treatment and sampling times at which the samples (broken) were taken.

5. For subject #40, the firm is requested to provide the reasons and complete information for the missing of the 36 hrs, 48 hrs and 60 hrs blood samples of period 1.

6. Comparative dissolution profiles for the lot used in this study and the one used in previous studies should be submitted for evaluation.

RECOMMENDATIONS:

The fasted in vivo bioequivalence study, protocol #10880: A SINGLE-DOSE, FASTING, TWO-PERIOD, IN VIVO BIOEQUIVALENCE STUDY IN 64 SUBJECTS, conducted by for Zenith Laboratories, Inc., on its nadolol tablets, 40 mg, lot #ND-047, versus the listed reference product, Corgard^{R} Tablets, 40 mg, Lot #1A61746, manufactured by Princeton/Squibb, have been found incomplete by the Division of Bioequivalence for the reasons stated in the Deficiencies above.

Nhan L. Tran, Ph.D.
Division of Bioequivalence
Review Branch II

In Vitro Dissolution Testing For 20 mg and 40 mg Tablets

Drug (Generic Name): Nadolol Tablets
Dose Strengths: 40 mg, 20 mg
ANDA No.: 74-229
Firm: Zenith Laboratories, Inc.
Submission Date: 5/6/93
File Name: 74229SDW.593

I. Conditions for Dissolution Testing:

Apparatus: USP XXII Basket
RPM: 100
No. Units Tested: 12
Medium: 0.1N HCL
Volume: 900 mL
Tolerance (USP): NLT ,Q) in 50 minutes
Reference Drug: Corgard[n] Tablets (Princeton)
Assay Methodology: per USP XXII

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # ND-048 Strength (mg): 20			Reference Product Lot # OA51800 Strength (mg): 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	59		14.5	45		26.5
15	94		6.3	78		12.0
30	97		2.0	97		1.9
50	97		1.8	99		2.7
60	97		1.7	98		1.0

Sampling Times (Minutes)	Test Product Lot # ND-047 Strength(mg): 40			Reference Product Lot # 1A61746 Strength(mg): 40		
	Mean %	Range	%CV	Mean %	Range	%CV
10	53.4		18.3	45.0		25.6
15	95.0		11.3	89.0		18.6
30	100.9		1.76	99.9		1.38
50	101.3		1.45	101.3		1.02
60	101.5		1.70	102.2		1.82

In Vitro Dissolution For 80 mg, 120 mg and 160 mg Tablets

Drug: Nadolol Tablets
Dose Strengths: 80 mg, 120 mg, 160 mg
ANDA: 74-255
Firm: Zenith Laboratories, Inc.

I. Conditions for Dissolution Testing:

Apparatus: USP 23 Basket; RPM: 100, No. Units Tested: 12
Medium: 0.1N HCL; Volume: 900 mL
Tolerance (USP): NLT (Q) in 50 minutes

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # ND-046 Strength: 80 mg			Reference Product Lot # OG51617 Strength: 80 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	62		6.9	50		14.5
15	83		6.6	71		11.0
30	98		2.1	94		6.9
50	98		2.2	96		1.8
60	98		2.7	96		0.9

Sampling Times (Minutes)	Test Product Lot # ND-049 Strength: 120 mg			Reference Product Lot # OG51762 Strength: 120 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	57		7.0	52		8.0
15	77		5.3	72		6.2
30	103		0.5	98		1.8
50	103		0.6	98		2.2
60	103		0.6	98		2.2

Sampling Times (Minutes)	Test Product Lot # ND-045 Strength: 160 mg			Reference Product Lot # OG51987 Strength: 160 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	53.7		6.7	45.5		6.4
20	86.8		5.7	74.9		5.0
30	100.4		1.4	95.5		3.2
50	101.1		0.8	98.3		1.1
60	100.9		0.8	98.5		1.2

COMPARATIVE FORMULATIONS* ZENITH'S NADOLOL TABLETS

COMPONENT	MG/TAB 20 MG TAB	W/W%	MG/TAB 40 MG TAB	W/W%
Nadolol, USP Citric Acid, USP Green Aluminium Lake Blend Povidone, USP Corn Starch, NF Microcrystalline Cellulose, NF Mag. Stearate, NF	20.00	13.3	40.00	13.3
Totals	150.00	100%	300.00	100%

	MG/TAB 80 MG TAB	W/W%	MG/TAB 120 MG TAB	W/W%	MG/TAB 160 MG TAB	W/W%
Nadolol, USP Citric Acid, USP Green Alum Lake Blend Povidone, USP Corn Starch, NF Microcrystalline Cellulose, NF Mag. Stearate, NF ***Sodium Starch Glycolate, NF***	80	17.4	120	17.4	160	17.4
Totals	460.00	100%	690.00	100%	920.00	100%

ANDA 74-229

APR - 3 1996

Zenith Laboratories, Inc.
Attention: Robert M. Monaghan
140 Legrand Avenue
Northvale, NJ 07647

Dear Sir:

Reference is made to the bioequivalence data submitted on October 20, 1995, for Nadolol Tablets USP, 20 mg and 40 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1.

2.

3.

4. For subject #29, please submit complete information concerning the broken samples: sample ID, period, treatment and sampling times at which the samples (broken) were taken.

5. For subject #40, please provide a complete explanation as to the reasons this patient missed the 36 hrs, 48 hrs and 60 hrs blood collection times during period 1.

6. Comparative dissolution profiles for the lot used in this study and the one used in previous studies should be submitted for evaluation.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DIV

AUG 2 3 1994

Nadolol
Tablets, 20 mg, 40 mg
ANDA #74-229
Reviewer: L.A. Ouderkirk
WP #74229S.093

Zenith Laboratories, Inc.
Northvale, New Jersey
Submission Date:
October 28, 1993
January 14, 1994

Review of Three Fasted In-Vivo Bioequivalence Studies and One Post-Prandial Bioequivalence Study

BACKGROUND:

Nadolol is a long-acting, synthetic, non-selective beta-adrenergic receptor blocker used to treat essential hypertension, cardiac arrhythmia, and angina pectoris. The absorption of nadolol from the G.I. tract is variable following oral dosing, averaging about 30%. About 20-30% of the drug is reversibly bound to plasma proteins. Peak blood serum concentrations are reached within one to four hours following oral administration. The elimination half-life is in the range of 12 to 24 hours, permitting once daily dosing. Because nadolol is excreted unchanged primarily in the urine, its half-life increases in patients with renal impairment. Pharmacokinetically, the drug is described by an open, two-compartment model. The approved labeling for the drug states that the presence of food in the G.I. tract does not affect the rate or extent of absorption and that nadolol may be dosed without regard to meals. The product is marketed as oral tablets in strengths of 20, 40, 80, 120, and 160 mg (Corgard®, Princeton Laboratories/Squibb).

APPROVAL REQUIREMENTS:

The Office of Generic Drugs issued an in vivo bioequivalence and in vitro dissolution guidance for nadolol tablets on 5/16/92. This guidance states that firms seeking approval for nadolol tablets in strengths of 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg should conduct a fasted bioequivalence study on the 160 mg strength and a fasted and post-prandial studies on the 40 mg strength. Provided the strengths are proportionally formulated and meet the dissolution standards, the in vivo bioequivalence requirements for the 20 mg, 80 mg, and 120 mg test product strengths can be waived.

SUBMISSION HISTORY:

The firm has previously submitted (11/19/92) bioequivalence study #10334A, a two-way fasted crossover design conducted on its 160 mg strength of nadolol tablets, ANDA 74-255. This study was reviewed by the Division and found acceptable; however, approval of ANDA 74-255 for nadolol strengths 160 mg, 120 mg, and 80 mg was

denied pending demonstration of comparable food effect (versus Corgard®) for either the 160 mg or 40 mg strength. If comparable food effect was to be demonstrated on the 40 mg strength, fasted bioequivalence for the 40 mg tablet would also be required to be demonstrated in order for the 160 mg, 120 mg, and 80 mg strengths to meet the bioequivalence requirements.

The firm subsequently submitted (5/6/93) study #10433, a single-dose three-way in vivo food effects study conducted on the 40 mg strength of the test product. The study was found acceptable, but the application was not approved and the waiver request was denied pending conduct of a fasted bioequivalence study for this strength.

In the present submissions under review, dated 10/28/93 and 1/14/94, the firm has submitted four additional in vivo bioequivalence studies to ANDA 74-229 for the 40 mg test product: (1) study #10333A (a two-way fasted crossover design using a 2 x 40 mg dose), (2) study #10511 (a fasted two-treatment, four-period replicate design using a 2 x 40 mg dose), (3) study #10468 (a full, two-treatment, two-period, post-prandial crossover design using a 2x40 mg dose), and (4) study #10591 (a fasted, two-treatment, two-period, crossover study in 58 subjects using a 4 x 40 mg dose).

SUMMARY OF SUBMISSION HISTORY AND FDA RECOMMENDATIONS:

A summary of the submission history and recommendations for Zenith nadolol tablets follows:

Present Studies:

	Study	Type	Dose	No. Subj.	FDA Recommendation
1)	10333A	Fasting	2x40 mg	35	Unacceptable
2)	10511	Fasting	2x40 mg	19	Unacceptable
3)	10468	(Full) Food	2x40 mg	36	Acceptable
4)	10591	Fasting	4x40 mg	57	Unacceptable

Past Studies:

5)	10433	(Limited) Food	2x40 mg	12	Acceptable
6)	10334A	Fasted	1x160 mg	35	Acceptable

Bioequivalence Approval Status:

7) ANDA #74-255 Nadolol Tablets, 160, 120, 80 mg - Unacceptable
8) ANDA #74-229 Nadolol Tablets, 40, 20 mg - Unacceptable

PROTOCOL FOR STUDY #10333A: A SINGLE-DOSE, FASTING, IN-VIVO BIOEQUIVALENCE STUDY IN 35 SUBJECTS:

A. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

The bioequivalence study was conducted at The principal investigator was

B. STUDY OBJECTIVE:

One objective of the study was to compare the rate and extent of absorption of the test versus the reference product under fasting conditions to determine if the test and reference formulations were bioequivalent.

C. STUDY DESIGN:

The study was designed as a random, two-period, two-treatment crossover using healthy male subjects.

D. SUBJECT SELECTION CRITERIA:

Subjects selected for the study met the following acceptance criteria:

1. Aged 19-50 years.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
3. No concurrent illness, acute or chronic diseases or history of asthma, unexplained syncope, myocardial ischemia, prostatic enlargement, bronchitis, rhinitis, diabetes, thyroid disease, or serious cardiovascular, renal, G.I., hepatic, or hematopoietic disease.
4. No history of alcohol or drug abuse.
5. No allergy to nadolol/beta blockers, atropine, epinephrine, or albuterol.
6. No evidence of hypoglycemia.
7. Normal electrocardiogram with no evidence of first degree AV block.
8. Resting B.P. and pulse rate of at least 100/60 mmHg and 55 bpm, respectively.
9. Weight within 15% of ideal for height (Metropolitan Life Insurance Company Bulletin, 1983).

E. SUBJECT RESTRICTIONS:

1. No alcohol consumption beginning 24 hours prior to dosing and lasting until 48 hours after.
2. No concurrent medication of any type.
3. No Rx or OTC drugs beginning two weeks prior to the study.
4. Controlled diet - no xanthines beginning 24 hours before dosing.

F. STUDY SCHEDULES:

Subjects were fasted for ten hours overnight prior to dosing. The volunteers were randomly numbered and divided into two dosing groups of equal number. An 80 mg (2x40 mg tablets) oral dose of the test product was administered with 240 ml of water in order of subject number. All of the subjects fasted until 5 hours post-dose, when a standard lunch was served. Water *ad lib* was permitted except within one hour of drug administration. Only the food served was permitted for 24 hours after dosing. Subjects were prohibited from smoking beginning 1 hour before dosing and lasting until 4 hours after dosing.

Blood pressure and pulse measurements were taken pre-dose and at 1, 2, 3, 4, 8, 12, 16, and 24 hours post-dose. Venous blood samples (10 ml) were drawn pre-dose (0 hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose. The blood samples were allowed to clot at room temperature for 30 minutes and were then centrifuged at 10^0 C. The separated serum was frozen at -20^0 C. within 24 minutes of centrifugation and stored until assayed. A two-week washout period was observed between study Phases.

G. DRUG TREATMENTS:

1. Test Treatment A: Nadolol Tablets, 2 X 40 mg, (Zenith), Lot # ND-047, Assayed Potency (n=30) = 101.0%, Exp. Date = 7/15/93, Lot Size =

2. Reference Treatment B: Corgard^R Tablets, 2 X 40 mg, (Princeton/Squibb), Lot # 1A61746, Assayed Potency (n=10) = 99.1%, Exp. Date = 1/1/96

H. CLINICAL NOTES:

Of the 38 subjects enrolled in the study, 35 completed both phases. The participation of subject #9 was discontinued for medical reasons. Subject #17 was disqualified 10 minutes before Phase 1 dosing and was not replaced. Subject #23 was withdrawn from the study prior to Phase 2 dosing for failure to return to the facility for check-in. The following schedule was observed:

Study Phase 1: October 8 - 12, 1992; Dosing date = 10/9/92
Study Phase 2: October 22 - 26, 1992; Dosing date = 10/23/92

The clinical samples were transferred from the clinic to the laboratory on October 27, 1992. The samples were stored at -20° C. Sample analyses were performed October 28 to November 13.

Eighteen adverse events were reported by a total of 15 subjects. Nine adverse events each were recorded for the test and reference products; all were judged mild in severity. Fourteen of the events were judged probably related to the study drug, one possibly related, and four unlikely to be related.

I. ASSAY METHOD PERFORMANCE AND VALIDATION STUDY:

J. ANALYTICAL:

K. STATISTICAL ANALYSIS:

The study data were analyzed by ANOVA and the F-test to determine statistically significant (α=0.05) differences between treatments, dosing sequence, subjects within sequence, and days of administration for areas under the curve (AUC), maximum serum drug levels (Cmax), time to maximum drug levels (Tmax), elimination constants (Kel) and half-life values (T 1/2). ANOVA was performed for subject serum drug concentrations at each sampling time and included all sums of squares (Types I-IV).

The 90% confidence intervals (two, one-sided tests procedure) were also calculated for the AUC and Cmax parameters. The statistical analysis was performed using SAS® version 6.07 and PROC GLM for the ANOVA. Since statistical evaluation of the 90% confidence intervals for limited food-effect studies is not required for bioequivalence determination, these data are not discussed in this review.

L. INFORMED CONSENT AND IRB APPROVAL:

Subjects gave written, informed consent prior to their acceptance into the study. The study protocol was reviewed and approved by an IRB prior to its initiation.

RESULTS OF BIOEQUIVALENCE STUDY #10333A:

The results of the bioequivalence study for 35 subjects are summarized in Tables 1 - 2 and Figure 1. The test and reference least-squares means for AUC(0-t), AUC(inf), and Cmax differed 6.4%, 3.5%, and 9.3%, respectively. The 90% confidence intervals for the test versus the reference products were 84-102% for LnAUC(0-t), 86-105% for LnAUC(Inf), and 77-103% for LnCmax.

PROTOCOL FOR STUDY #10511: A SINGLE-DOSE, FASTING, FOUR-PERIOD, REPLICATE-DESIGN, IN VIVO BIOEQUIVALENCE STUDY IN 19 SUBJECTS:

The protocol for study #10511 is the same as that for the study #10333A, above, except for the following:

A. STUDY DESIGN:

The study was designed as a random, fasted, two-treatment, four-period crossover (replicate design) using 19 healthy male subjects.

B. STUDY SCHEDULES:

Twenty-four subjects were enrolled and there was no 72 hour blood collection.

C. CLINICAL NOTES:

Of the 24 subjects enrolled in the study, 19 completed both phases. Subjects #14, #17, and #19 were withdrawn from the study due to a positive drug screen. Subject #18 was withdrawn because he did not wish to continue in the study. Subject #22 was withdrawn for failure to return to the facility for Phase II. The following schedule was observed:

Study Phase 1: April 27 - 30, 1993; Dosing date = 4/28/93
Study Phase 2: May 11 - 14, 1993; Dosing date = 5/13/93
Study Phase 3: May 25 - 28, 1993; Dosing date = 5/26/93
Study Phase 4: June 8 - 11, 1993; Dosing date = 6/26/93

The clinical samples were transferred from the clinic to the laboratory on June 15, 1993. The samples were stored at -20^{0} C. Analysis took place July 6-22, 1993.

Twenty-five adverse events were reported by a total of 12 subjects. Ten adverse events were recorded for the test product and fifteen for the reference. All were judged mild or moderate in severity. Eighteen of the events were judged possibly related to the study drug, two probably related, and five unrelated.

D. ANALYTICAL:

RESULTS OF BIOEQUIVALENCE STUDY #10511:

The results of bioequivalence study for 19 subjects are summarized in Tables 3 - 4 and Figure 2. The test and reference least-squares means for AUC(0-t), AUC(inf), and Cmax differed 3.8%, 2.2%, and 18%, respectively. The 90% confidence intervals for the test versus the reference products were 93-101% for LnAUC(0-t), 92-109% for LnAUC(Inf), and 96-126% for LnCmax.

PROTOCOL FOR STUDY #10468: A SINGLE-DOSE, TWO-PERIOD, TWO-TREATMENT, IN VIVO, POST-PRANDIAL BIOEQUIVALENCE STUDY IN 36 SUBJECTS:

The protocol for study #10511 was the same as that for the study #10333A, above, except for the following:

A. STUDY OBJECTIVE:

One objective of the study was to determine if the in vivo absorption of the test and reference products was similar when the products were given immediately after a meal. A second objective was to compare the absorption of the test product when dosed under fed versus fasted conditions.

B. STUDY DESIGN:

The study was designed as a random, two-treatment, two-period, post-prandial crossover using healthy male subjects.

C. STUDY SCHEDULES:

Subjects were fasted for ten hours overnight prior to dosing. The volunteers were randomly numbered and divided into two dosing groups of equal number.

Subjects were given 30 minutes to consume a standard breakfast consisting of one fried egg, one buttered English muffin, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 180 ml of orange juice and 240 ml of whole milk. After an additional 5 minutes, the subjects were administered an 80 mg oral dose (2 x 40 mg tablets) of the test or reference product with 240 ml of water. All of the subjects fasted until 5 hours post-dose, when a standard lunch was served. Water *ad lib* was permitted except within one hour of drug administration. Only the food served was permitted for 24 hours after dosing.

Blood pressure and pulse measurements were taken pre-dose and at 1, 2, 3, 4, 8, 12, 16, and 24 hours post-dose. Venous blood samples (10 ml) were drawn pre-dose (0 hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose. The blood samples were allowed to clot at room temperature for 30 minutes and were then centrifuged at 10° C. The separated serum was frozen at -20° C. within 24 minutes of centrifugation and stored until assayed. A two-week washout period was observed between Phase 1 and 2 dosing.

D. DRUG TREATMENTS:

1. Test Treatment A (Fed): Nadolol Tablets, 2 X 40 mg, (Zenith), Lot # ND-047, Assayed Potency (n=30) = 101.0%, Exp. Date = 7/15/93, Lot Size =

2. Reference Treatment B (Fed): Corgard® Tablets, 2 X 40 mg, (Princeton), Lot # 1A61746, Assayed Potency (n=10) = 99.1%, Exp. Date = 1/1/96

All of the subjects fasted until 5 hours post-dose, when a standard lunch was served. Water *ad lib* was permitted except within one hour of drug administration. Only the food served was permitted for 24 hours after dosing. Subjects were prohibited from smoking beginning 1 hour before dosing and lasting until 4 hours after dosing.

Blood pressure and pulse measurements were taken pre-dose and at 1, 2, 3, 4, 8, 12, 16, and 24 hours post-dose. Venous blood samples (10 ml) were drawn pre-dose (0 hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose. The blood samples were allowed to clot at room temperature for 30 minutes and were then centrifuged at 10^0 C. The separated serum was frozen at -20^0 C. within 24 minutes of centrifugation and stored until assayed. A two-week washout was observed between study Phases.

E. CLINICAL NOTES:

Of the 38 subjects enrolled in the study, 35 completed the entire study and one, subject #9, completed all but the last four sample collections of Phase 2. Two subjects, #2 and #37, were withdrawn from the study prior to Phase 2 dosing for failure to comply with the protocol. The following schedule was observed:

Study Phase 1: February 10 - 14, 1993; Dosing date = 2/11/93
Study Phase 2: February 24 - 28, 1993; Dosing date = 2/25/93

The clinical samples were transferred from the clinic to the laboratory on March 8, 1993. The samples were stored at -20^0 C. Analysis took place April 2 - 27, 1993.

Twenty-three adverse events were reported by a total of sixteen subjects. Fourteen adverse events were recorded for the test product and nine for the reference. All were judged mild or moderate in severity. Four of the events were judged possibly related to the study drug, fourteen probably related, and five unrelated.

F. ANALYTICAL:

G. ASSAY METHOD PERFORMANCE AND VALIDATION STUDY:

RESULTS OF IN VIVO POST-PRANDIAL STUDY #10468:

The results of the bioequivalence study for 36 subjects is summarized in Tables 5 - 6 and Figure 3. The test and reference least-squares means for AUC(0-t), AUC(inf), and Cmax differed 0.0%, 1.3% and 6.4%, respectively. The 90% confidence intervals for the test versus the reference products were 93 - 104% for LnAUC(0-t), 96 - 107% for LnAUC(Inf), and 97 - 108% for LnCmax.

PROTOCOL FOR STUDY #10591: A SINGLE-DOSE, FASTING, TWO-PERIOD, IN VIVO BIOEQUIVALENCE STUDY IN 57 SUBJECTS:

The protocol for study #10591 is the same as that for the study #10333A, above, except for the following:

A. STUDY DESIGN:

The study was designed as a random, fasted, two-treatment crossover using two dosing groups of healthy male subjects.

B. CLINICAL NOTES:

Of the 64 subjects enrolled in the study, 58 completed both

phases. Subjects #20, #24, and #26 failed to return to the facility for Study Phase 2. Subject #39 was withdrawn from the study prior to Phase 2 due to an injury received during the interim washout period between study phases. Subject #14 was withdrawn from the study by the physician because of an elevated oral temperature recorded prior to phase 2 dosing. Subject #45 was withdrawn by the physician following the 2.5 hour blood sample collection in Phase 1 due to a vasovagal response experienced at that time.

Dosing Group #1 (Subjects #1-#29):

Study Phase 1: October 8-11, 1993; Dosing date = 10/9/93
Study Phase 2: October 22-25, 1993; Dosing date = 10/23/93

Dosing Group #2 (Subjects #30-#64):

Study Phase 1: November 5-8, 1993; Dosing date = 11/6/93
Study Phase 2: November 19-22, 1993; Dosing date = 11/20/93

Twenty-eight subjects reported a total of 48 adverse events during the study. Of the three judged severe, none was determined to be related to the study medications.

B. ASSAY METHOD PERFORMANCE AND VALIDATION STUDY:

C. ANALYTICAL:

D. STATISTICAL ANALYSIS:

Because of the relatively large number of subjects who participated in this study, the volunteers were divided into two separate groups who were dosed at different times (see Clinical Notes section, above). Consequently, the statistical analysis for this study included a sequence-by-group factor to determine if there were any effects of dosing group on the study results.

RESULTS OF BIOEQUIVALENCE STUDY:

The results of the bioequivalence study for 57 subjects are summarized in Tables 7 - 8 and Figure 4. The least-squares means for AUC(0-t), AUC(inf), and Cmax differed 2% between the test and reference products. The 90% confidence intervals for the test versus the reference products were 96-110% for LnAUC(0-t) and LnAUC(Inf), and 94-115% for LnCmax.

DEFICIENCIES:

1. The fasted in vivo bioequivalence study #10333A demonstrates that the test and reference products are absorbed to an equivalent extent, as measured by the LnAUC 90% confidence intervals. The rate of absorption of the test product, however, was significantly slower than that of the reference, as measured by the LnCmax 90% confidence intervals.

2. The fasted in vivo bioequivalence study #10511 demonstrates that the test and reference products are absorbed to an equivalent extent, as measured by the LnAUC 90% confidence intervals. The rate of absorption of the test product, however, was significantly faster than that of the reference, as measured by the LnCmax 90% confidence intervals.

3. In the fasted in vivo bioequivalence study #10591, the firm administered a 160 mg dose (4 x 40 mg tablets) to the study participants, rather than the 2 x 40 mg dose used in the firm's failed studies #10333A and #10511, without justifying this change in study design. Though the study #10591 technically meets the Division's 90% confidence interval criteria for AUC and Cmax, (extent and rate of absorption), the study design is unacceptable and the study fails to demonstrate the bioequivalence of the firm's 40 mg nadolol tablets as follows:

a.) The firm has twice failed to establish the bioequivalence of its 40 mg nadolol tablet when given as 2 x 40 mg oral doses.

b.) The kinetics of nadolol have not been shown to be linear at oral doses exceeding 80 mg.

c.) Based on (a) and (b), above, the study #10591 fails to demonstrate the bioequivalence of the firm's 40 mg tablets at dosing levels of 2 x 40 mg or lower.

RECOMMENDATIONS:

1. The fasted in vivo bioequivalence studies #10333A, #10511, and #10591, conducted by Zenith Laboratories, Inc., on its nadolol tablets, 40 mg, lot #ND-047, versus the listed reference product, Corgard® Tablets, 40 mg, Lot #1A61746, manufactured by Princeton/Squibb, have been found unacceptable by the Division of Bioequivalence for the reasons stated in the

Deficiencies, above.

2. The post-prandial in vivo bioequivalence study #10468, conducted by Zenith Laboratories on its nadolol tablets, 40 mg, lot #ND-047, versus the listed reference product, Corgard® Tablets, 40 mg, Lot #1A61746, manufactured by Princeton/Squibb, has been found acceptable. The study demonstrates that Zenith's nadolol tablets, 40 mg, are absorbed at a rate and to an extent equivalent to that of the reference product, when both are dosed under post-prandial conditions.

3. From the Bioequivalence viewpoint, the firm has not met the in vivo bioequivalence requirements for its nadolol tablets, 40 mg and the ANDA 74-229 is unacceptable.

The firm should be advised of the Deficiencies, Comments, and Recommendations, above.

6/30/94

Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

RD INITIALED ATWU
FT INITIALED ATWU

Concur: _____ Date: 8/23/94

Ramakant M. Mhatre, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 74-255 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CVishwanathan), HFD-652 (Wu, Ouderkirk), Drug File, Division File

TABLE 1

IN VIVO FASTED BIOEQUIVALENCE STUDY #10333A
ARITHMETIC MEAN NADOLOL SERUM CONCENTRATIONS (NG/ML)
IN 35 SUBJECTS FOLLOWING A 2X40 MG DOSE

Hours	Test Product	Reference Product	T/R
0	0.0	0.0	---
0.5	26.4 (70)*	15.4 (66)	1.71
1	65.0 (62)	64.4 (65)	1.01
1.5	80.1 (58)	82.3 (63)	0.97
2	94.2 (52)	94.4 (57)	1.00
2.5	105 (50)	113 (53)	0.93
3	114 (47)	119 (48)	0.96
4	111 (56)	126 (43)	0.88
5	104 (54)	115 (45)	0.90
6	87.4 (47)	93.4 (43)	0.94
8	68.7 (40)	72.6 (38)	0.95
12	50.7 (39)	54.1 (36)	0.94
16	39.1 (38)	41.9 (36)	0.93
24	29.0 (35)	30.7 (33)	0.94
36	15.9 (40)	16.5 (41)	0.96
48	8.94 (61)	9.57 (59)	0.93
60	2.75 (157)	4.61 (92)	0.60
72	2.35 (396)	1.26 (210)	1.87

* (C.V.%)

TABLE 2

A. PHARMACOKINETIC LEAST SQUARES MEANS (STD. ERROR)
FASTED STUDY #10333A IN 35 SUBJECTS, 2X40 MG DOSE

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	1853 (77)	1979 (77)	0.94
AUC(0-∞) [ng/mlxhr]	2070 (87)	2145 (87)	0.97
Cmax [ng/ml]	138 (8.0)	152 (8.0)	0.91
Tmax [Hrs.]	3.13 (0.16)	3.45 (0.16)	0.91
T1/2 [Hrs.]	15.4 (0.285)	15.5 (0.275)	0.99
Kel [Hr^{-1}]	0.0481 (0.00088)	0.0478 (0.00088)	1.01

B. PHARMACOKINETIC ARITHMETIC MEANS (C.V.%)

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	1856 (39)	1989 (37)	0.94
AUC(0-∞) [ng/mlxhr]	2070 (39)	2154 (36)	0.97
Cmax [ng/ml]	139 (43)	153 (39)	0.91
Tmax [Hrs.]	3.10 (43)	3.44 (32)	0.91
T1/2 [Hrs.]	15.3 (26)	15.5 (25)	0.99
Kel [Hr^{-1}]	0.0483 (27)	0.0477 (26)	1.01

C. 90% CONFIDENCE INTERVALS

Parameter	90% Confidence Interval*
Ln AUC(0-T) [ng/ml x hr]	84 - 102%
Ln AUC(0-∞) [ng/ml x hr]	86 - 105%
Ln Cmax [ng/ml]	77 - 103%

* Confidence Intervals Verified by Reviewer

TABLE 2

A. **PHARMACOKINETIC LEAST SQUARES MEANS (STD. ERROR) FASTED STUDY #10333A IN 35 SUBJECTS, 2X40 MG DOSE**

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	1853 (77)	1979 (77)	0.94
AUC(0-∞) [ng/mlxhr]	2070 (87)	2145 (87)	0.97
Cmax [ng/ml]	138 (8.0)	152 (8.0)	0.91
Tmax [Hrs.]	3.13 (0.16)	3.45 (0.16)	0.91
T1/2 [Hrs.]	15.4 (0.285)	15.5 (0.275)	0.99
Kel [Hr^{-1}]	0.0481 (0.00088)	0.0478 (0.00088)	1.01

B. **PHARMACOKINETIC ARITHMETIC MEANS (C.V.%)**

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	1856 (39)	1989 (37)	0.94
AUC(0-∞) [ng/mlxhr]	2070 (39)	2154 (36)	0.97
Cmax [ng/ml]	139 (43)	153 (39)	0.91
Tmax [Hrs.]	3.10 (43)	3.44 (32)	0.91
T1/2 [Hrs.]	15.3 (26)	15.5 (25)	0.99
Kel [Hr^{-1}]	0.0483 (27)	0.0477 (26)	1.01

C. **90% CONFIDENCE INTERVALS**

Parameter	90% Confidence Interval*
Ln AUC(0-T) [ng/ml x hr]	84 - 102%
Ln AUC(0-∞) [ng/ml x hr]	86 - 105%
Ln Cmax [ng/ml]	77 - 103%

* Confidence Intervals Verified by Reviewer

TABLE 3

IN VIVO FOUR-PERIOD FASTED BIOEQUIVALENCE STUDY #10511
ARITHMETIC MEAN NADOLOL SERUM CONCENTRATIONS (NG/ML)
2 x 40 MG DOSE ADMINISTERED TO 19 SUBJECTS

Hours	Test Product	Reference Product	T/R
0	0.0	0.0	---
0.5	34.9 (46)*	20.8 (35)	1.68
1	85.5 (33)	74.7 (30)	1.14
1.5	100 (44)	101 (35)	0.99
2	108 (37)	110 (34)	0.98
2.5	121 (49)	115 (32)	1.05
3	150 (83)	121 (32)	1.24
4	150 (62)	124 (45)	1.21
6	108 (49)	100 (32)	1.08
8	83.1 (43)	79.4 (25)	1.05
12	59.9 (36)	57.1 (25)	1.05
16	46.5 (35)	43.6 (28)	1.07
24	32.2 (33)	31.5 (23)	1.02
36	17.2 (27)	18.9 (23)	0.91
48	9.73 (31)	11.4 (37)	0.85
60	2.75 (157)	6.00 (65)	0.46

* (C.V.%)

FIGURE 1

Mean Nadolol Serum Levels

n = 35

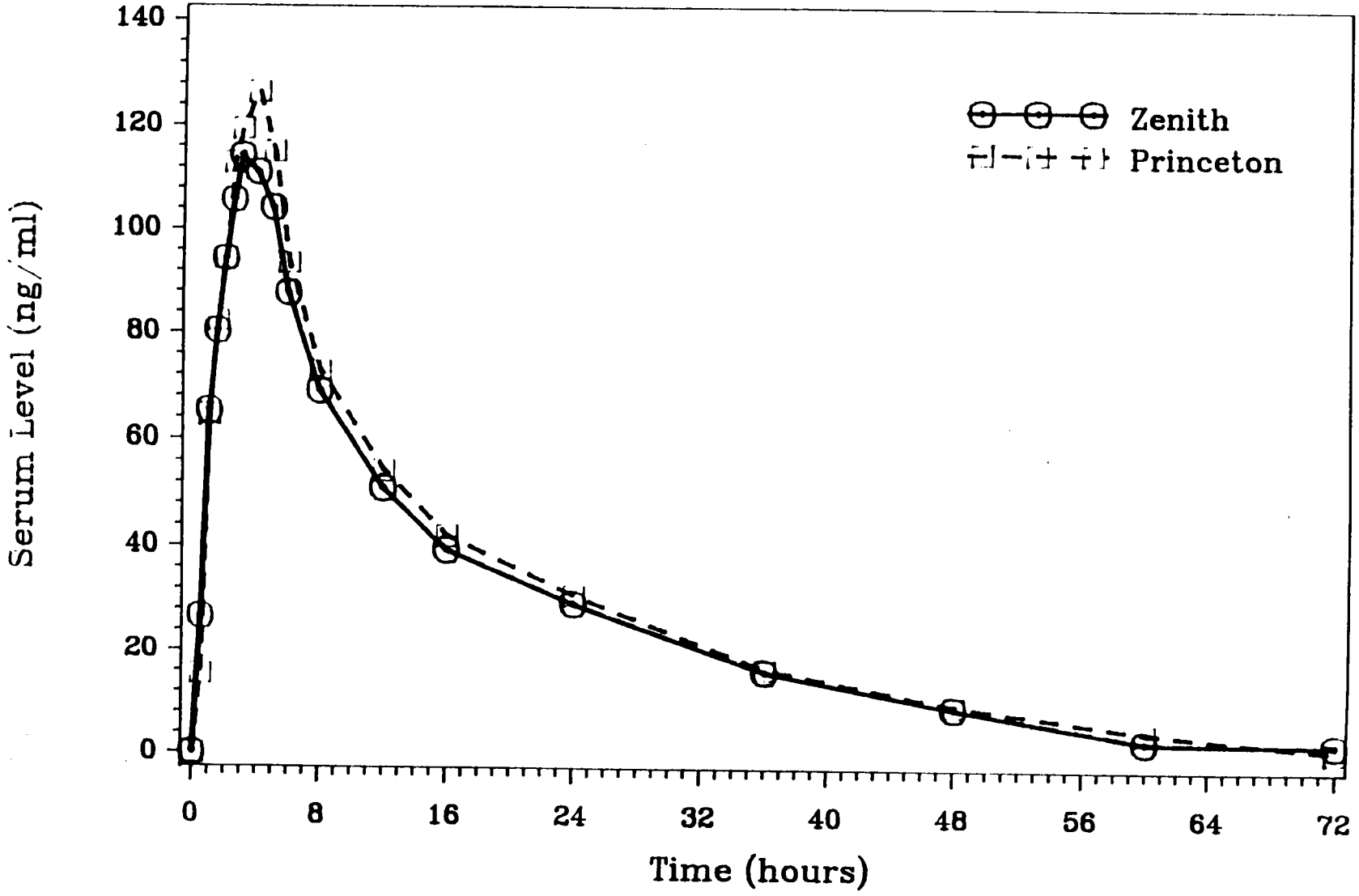


FIGURE 2

Mean Nadolol Serum Levels

Number of Subjects = 19
(38 Observations)

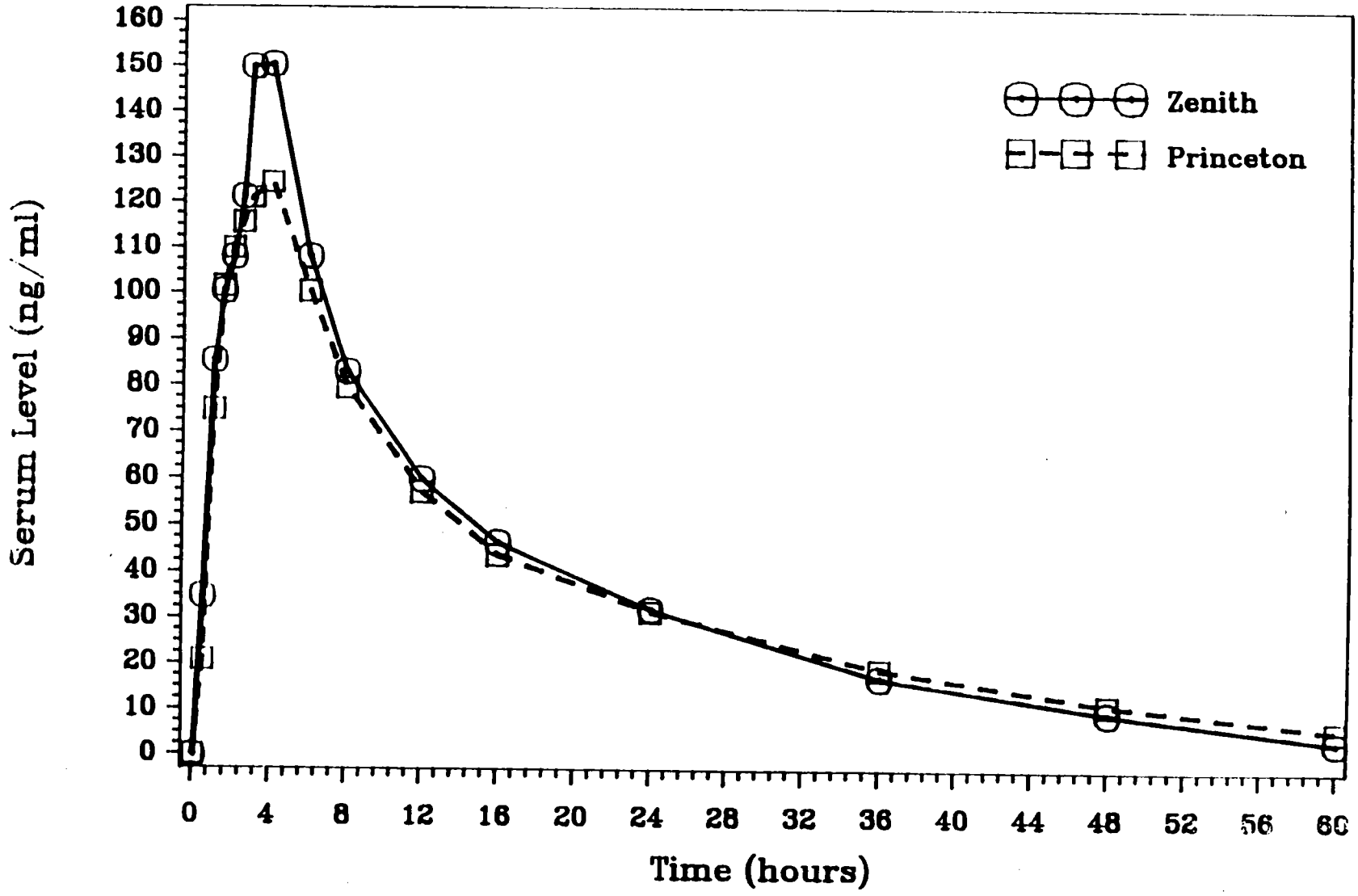


TABLE 4

A. FASTED FOUR-PERIOD BIOEQUIVALENCE STUDY #10511
PHARMACOKINETIC LEAST SQUARES MEANS (STD. ERROR)
2 x 40 MG DOSE ADMINISTERED TO 19 SUBJECTS

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	2211 (86)	2130 (85)	1.04
AUC(0-∞) [ng/mlxhr]	2415 (93)	2362 (91)	1.02
Cmax [ng/ml]	189 (12)	160 (12)	1.18
Tmax [Hrs.]	2.90 (0.17)	3.14 (0.16)	0.92
T1/2 [Hrs.]	14.7 (0.536)	16.8 (0.528)	0.88
Kel [Hr^{-1}]	0.0499 (0.00125)	0.0444 (0.00124)	1.12

B. PHARMACOKINETIC ARITHMETIC MEANS (C.V.%)
N=19 SUBJECTS

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	2150 (38)	2084 (25)	1.03
AUC(0-∞) [ng/mlxhr]	2352 (35)	2316 (25)	1.02
Cmax [ng/ml]	183 (66)	155 (34)	1.18
Tmax [Hrs.]	2.88 (36)	3.11 (40)	0.93
T1/2 [Hrs.]	14.8 (24)	16.9 (20)	0.88
Kel [Hr^{-1}]	0.0498 (23)	0.0441 (24)	1.13

C. 90% CONFIDENCE INTERVALS
N=19 SUBJECTS

Parameter	90% Confidence Interval*
Ln AUC(0-T) [ng/ml x hr]	93 - 111%
Ln AUC(0-∞) [ng/ml x hr]	92 - 109%
Ln Cmax [ng/ml]	96 - 126%

* Confidence Intervals Verified by Reviewer

TABLE 5

MEAN NADOLOL SERUM CONCENTRATIONS (NG/ML)
POST-PRANDIAL STUDY #10468
2 x 40 MG DOSE ADMINISTERED TO 36 SUBJECTS

Hours	Test Product	Reference Product	T/R
0	0.0	0.0	---
0.5	1.99 (233)*	0.42 (428)	4.76
1	23.4 (21)	17.5 (84)	1.34
1.5	54.0 (66)	49.4 (45)	1.09
2	72.5 (58)	68.0 (38)	1.07
2.5	78.2 (49)	74.7 (37)	1.05
3	80.8 (44)	79.2 (38)	1.02
4	73.9 (43)	72.7 (39)	1.02
5	62.9 (39)	64.6 (38)	0.97
6	54.8 (35)	55.8 (35)	0.98
8	49.6 (29)	49.3 (30)	1.01
12	39.9 (30)	40.1 (30)	1.00
16	32.3 (27)	31.8 (29)	1.02
24	23.9 (33)	24.3 (31)	0.98
36	14.3 (41)	13.8 (42)	1.04
48	7.94 (61)	7.84 (65)	1.01
60	4.04 (120)	4.09 (135)	0.99
72	1.31 (210)	1.50 (198)	0.87

* (C.V.%)

FIGURE 3

Mean Nadolol Serum Levels

n = 36

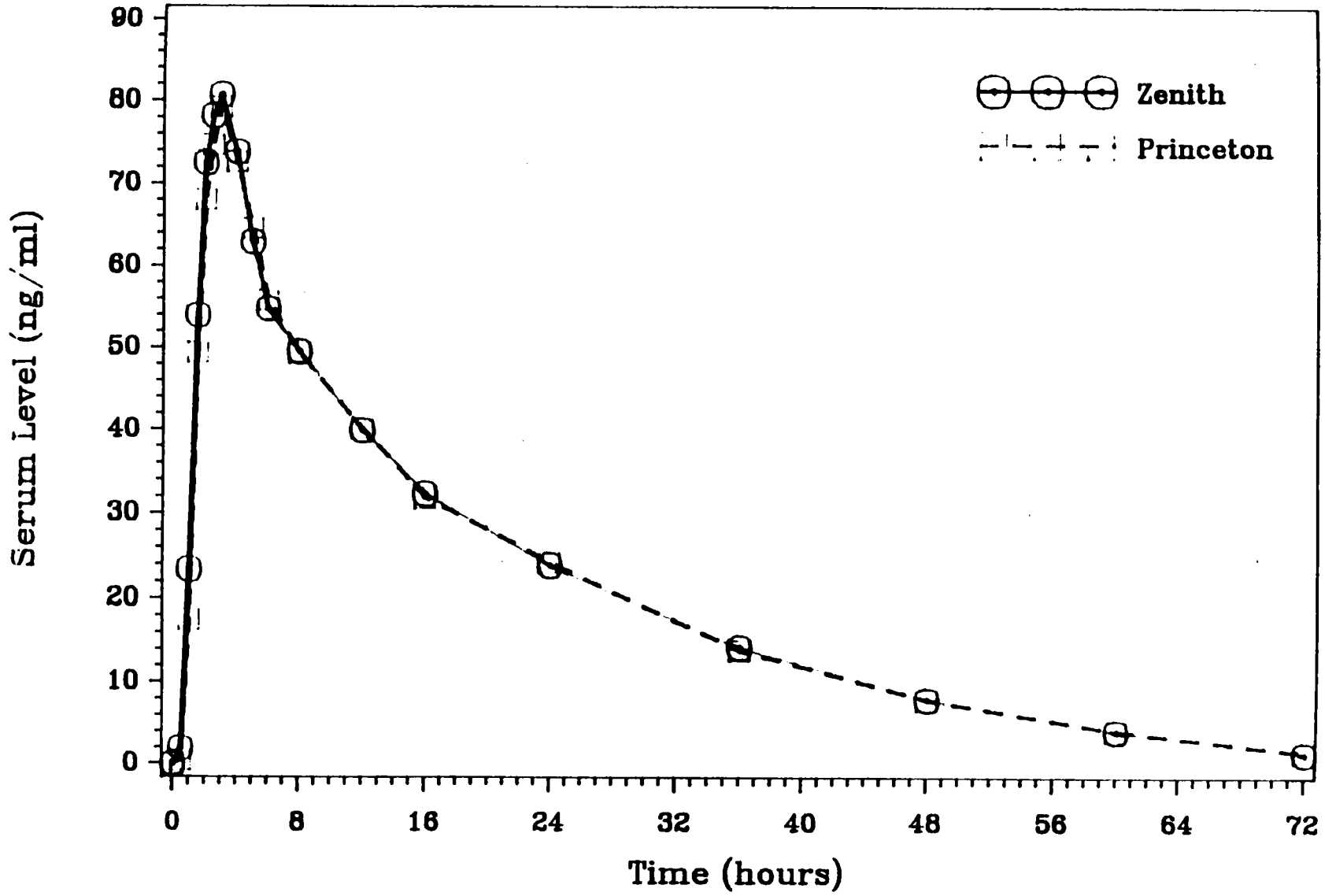


TABLE 6
POST-PRANDIAL STUDY #10468

A. PHARMACOKINETIC LEAST SQUARES MEANS (STD. ERROR)
N=36 SUBJECTS

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	1410 (27)	1408 (34)	1.00
AUC(0-∞) [ng/mlxhr]	1603 (33)	1581 (34)	1.01
Cmax [ng/ml]	90.6 (2.27)	85.1 (2.27)	1.06
Tmax [Hrs.]	2.99 (0.166)	2.96 (0.166)	1.01
T1/2 [Hrs.]	17.4 (0.443)	17.0 (0.456)	1.02
Kel [Hr^{-1}]	0.0420 (0.00124)	0.0437 (0.00128)	0.96

B. PHARMACOKINETIC ARITHMETIC MEANS (C.V.%)
N=36 SUBJECTS

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	1410 (36)	1408 (25)	1.00
AUC(0-∞) [ng/mlxhr]	1603 (32)	1579 (32)	1.02
Cmax [ng/ml]	90.6 (45)	85.1 (34)	1.06
Tmax [Hrs.]	2.99 (40)	2.96 (31)	1.01
T1/2 [Hrs.]	17.4 (24)	17.0 (26)	1.02
Kel [Hr^{-1}]	0.0420 (22)	0.0437 (27)	0.96

C. 90% CONFIDENCE INTERVALS
N=36 SUBJECTS

Parameter	90% Confidence Interval*
Ln AUC(0-T) [ng/ml x hr]	93 - 104%
Ln AUC(0-∞) [ng/ml x hr]	96 - 107%
Ln Cmax [ng/ml]	97 - 108%

* Confidence Intervals Verified by Reviewer

TABLE 7

MEAN NADOLOL SERUM CONCENTRATIONS (NG/ML)
FASTING STUDY #10591
2 x 40 MG DOSE ADMINISTERED TO 57 SUBJECTS

Hours	Test Product	Reference Product	T/R
0	0.0	0.134	---
0.5	59.1 (62)*	42.0 (78)	1.41
1	166 (87)	129 (60)	1.29
1.5	225 (62)	205 (71)	1.10
2	288 (68)	267 (71)	1.08
2.5	323 (57)	336 (62)	0.96
3	347 (57)	373 (57)	0.93
4	354 (59)	352 (58)	1.01
5	304 (52)	324 (59)	0.94
6	257 (53)	255 (52)	1.01
8	187 (41)	187 (46)	1.00
12	137 (43)	132 (41)	1.04
16	105 (39)	101 (39)	1.04
24	74.0 (49)	71.6 (42)	1.03
36	36.9 (40)	37.7 (52)	0.98
48	22.1 (55)	20.8 (50)	1.06
60	11.4 (60)	10.5 (64)	1.09

* (C.V.%)

FIGURE 4

Mean Nadolol Serum Levels

n = 57

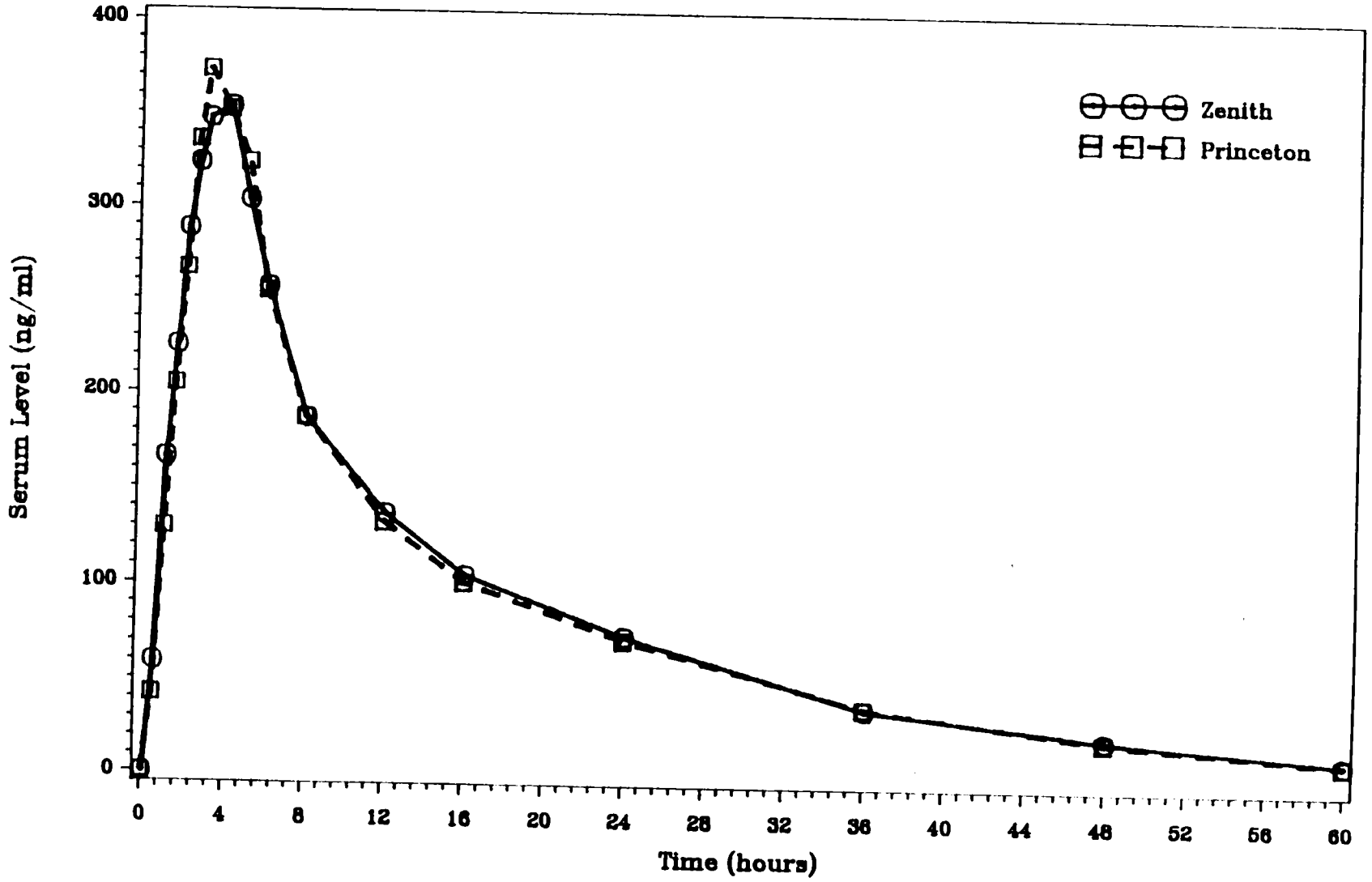


TABLE 8
STUDY #10591

A. PHARMACOKINETIC LEAST SQUARES MEANS (STD. ERROR)
N=57 SUBJECTS

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	5070 (141)	4985 (141)	1.02
AUC(0-∞) [ng/mlxhr]	5337 (143)	5249 (143)	1.02
Cmax [ng/ml]	472 (19.7)	462 (19.7)	1.02
Tmax [Hrs.]	3.27 (0.132)	3.40 (0.132)	0.96
T1/2 [Hrs.]	14.2 (0.265)	14.1 (0.265)	1.01
Kel [Hr^{-1}]	0.0515 (0.00079)	0.0517 (0.00079)	1.00

B. PHARMACOKINETIC ARITHMETIC MEANS (C.V.%)
N=57 SUBJECTS

Parameter	Test Product	Reference Product	T/R
AUC(0-T) [ng/mlxhr]	5086 (40)	4983 (42)	1.02
AUC(0-∞) [ng/mlxhr]	5350 (40)	5248 (40)	1.02
Cmax [ng/ml]	474 (50)	463 (51)	1.02
Tmax [Hrs.]	3.28 (34)	3.39 (37)	0.97
T1/2 [Hrs.]	14.1 (25)	14.1 (26)	1.00
Kel [Hr^{-1}]	0.0516 (21)	0.0517 (21)	1.00

C. 90% CONFIDENCE INTERVALS
N=57 SUBJECTS

Parameter	90% Confidence Interval*
Ln AUC(0-T) [ng/ml x hr]	96 - 110%
Ln AUC(0-∞) [ng/ml x hr]	96 - 110%
Ln Cmax [ng/ml]	94 - 115%

* Confidence Intervals Verified by Reviewer